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Archives of Internal Medicine

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RENAL IRRITATION IN MAN FROM HIGH PROTEIN DIET *

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In 1918 it was shown by one of us [1] that a high protein diet over long periods produced in rabbits chronic, diffuse, bilateral kidney lesions. It seemed not improbable, then, to expect some evidence of renal irritation if high protein diets were forced for short periods in those cases where some kidney damage already might exist.

In recent years a number of investigators have become more and more convinced that cases of so called essential hypertension were in fact nephritic. Harpuder [2] made a careful clinical and anatomic study of cases of essential hypertension and concluded that in every case a persistent hypertension was indicative of chronic nephritis of "arteriosclerotic type." Clinically, out of 504 cases with a systolic blood pressure persistently over 160 mm. mercury, 490, or 97.2 per cent. showed, definite disturbances of kidney function. But this view is not as yet universally accepted. Moschowitz,[3] for example, maintains that hypertension is not an outcome of nephritis but rather the response to continuous circulatory vasoconstricting influences and the kidney lesions result from the hypertension.

Inasmuch as the usual functional kidney tests fail in a certain percentage of cases of hypertension to give any evidence of kidney damage, we attempted to obtain such evidence by throwing an extra load on that organ. It seemed not improbable to expect some evidence of renal irritation if protein diets were forced for short periods in those cases in which some kidney damage already might exist.

PART 1

The patients used in the first part of this study were ordinary ward patients whose chief complaints centered about symptoms resulting from hypertension. For obvious reasons, the number of cases studied

* From the Department of Internal Medicine, Medical School, University of Michigan.

1. Newburgh, L. H.: The Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. **24**:359 (Oct.) 1919.

2. Harpuder, K.: Arteriosclerose, Schrumpfniere u. Blutdruck, Deutsch. Arch. f. klin. Med. **129**:44, 1918.

3. Moschowitz, E.: Hypertension: Its Significance, Relation to Arteriosclerosis and Nephritis and Etiology, Am. J. M. Sc. **158**:668, 1919.

was kept as small as was deemed consistent with conclusive results. Phenolsulphonephthalein elimination varied in the cases studied between 20 and 45 per cent. in two hours, and the blood urea nitrogen, determined by the Van Slyke method, varied between 9.8 and 13.0 mg. Preceding the high meat diet each patient was put on a low protein salt free diet for a period of from 5 to 10 days, during which time careful daily urinalyses were made. In Case 1, a trace of albumin was persistently present in the urine, but in the other cases albumin was absent. Occasional hyalin casts were found in all. In no case were red blood corpuscles found at any time preceding the high meat diet, and it should be emphasized at this point that in every case a careful daily search, with a 4 mm. objective, was made for such cells. A ward record was kept of the amount of protein actually eaten. During the low protein period this averaged 33 gm. in twenty-four hours, while on the forced protein diet from 100 to 175 gm. protein was ingested each day. A summary of the cases so studied follows:

REPORT OF CLINICAL OBSERVATIONS

CASE 1.—Female, aged 48, entered the hospital complaining of dizziness, periods of syncope, hot flashes and black spots before the eyes. She was married at 18, and had no pregnancies. The menopause occurred at 47. There was no history of scarlet fever or sore throat. She has had frontal headaches for the last twenty-five years. Nocturia has been present three times each night since childhood. Several months ago, systolic pressure was 260 mm.

Physical Examination.—On examination, the teeth were found to be carious and the tonsils atrophic. The left border of the heart was 10.5 cm. to the left of the midsternal line. No murmurs were heard at the apex. At the aortic area there was a high-pitched shrill crescendo systolic murmur ending in a bell-like second sound. The orthodiagram revealed a tortuous arch with some pushing downward of the heart but the heart area was normal. Very slight edema of both ankles was present. Fundus examination showed neuroretinitis with hemorrhages in the retina and degenerative changes about the macula. Her urine at entrance showed a faint trace of albumin, occasional granular casts, many white blood cells and no red blood cells. Blood pressure was 245/190. Phenolsulphonephthalein elimination was 10 per cent. the first hour and 10 per cent. the second hour. Blood urea nitrogen was 9.8 mg.

May 27, she was given a Mosenthal test meal. The specific gravity of the urine varied from 1.012 to 1.016, showing definite fixation.

Clinical Observation.—On admission she was placed on a salt free diet giving 34 gm. protein. After nine days of this diet, with rest in bed, her diastolic pressure had fallen from 190 to 140 mm. but the systolic pressure remained practically unchanged.

Starting May 29 she was given a high protein, salt poor diet, containing from 140 to 180 gm. protein daily. The urine at the beginning contained 0.5 gm. albumin per liter, and many white blood cells and hyalin casts, but no red blood cells. For a long period the urine showed no marked change, but the blood urea nitrogen gradually increased, being 12.1 mg. after five days of high protein, 21 mg. after ten days (June 7) and 25 mg. after nineteen days (June 16). June 18, twenty-one days after high protein was started, there was a decided increase in albumin to 2 gm. per liter, and three days

later (June 21) a few red blood cells[4] were found for the first time in her urine. Simultaneously with the urinary changes, definite edema appeared with distinct pitting of the ankles and her weight increased from 123 pounds, June 17, to 129 pounds June 24.

During the period of high protein diet, three fundus examinations were made in the department of ophthalmology. June 1 and June 9 no changes were found in the condition of the fundus as originally reported. June 21, following the

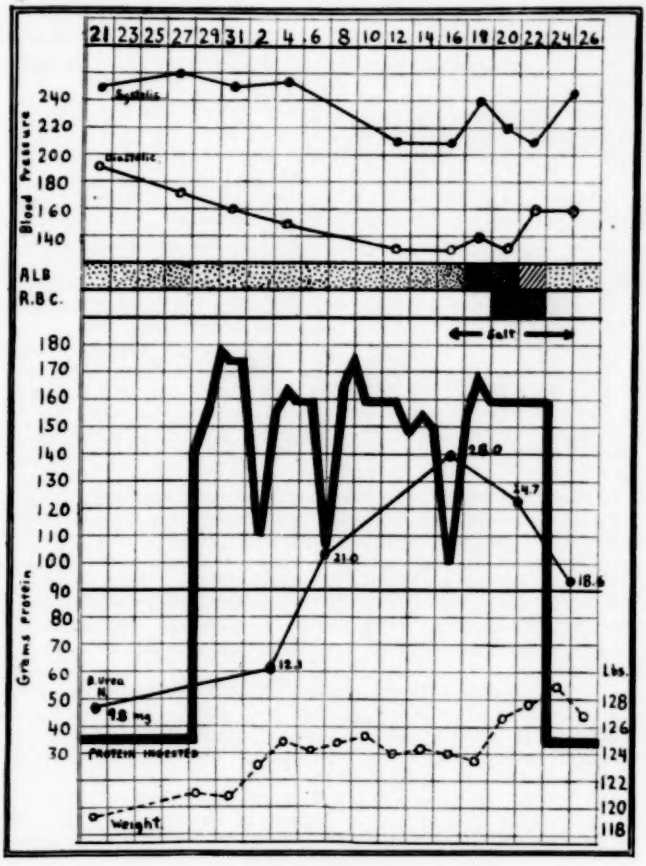

Chart 1.—Case 1.

appearance of red blood corpuscles in the urine, the fundus examination showed macular changes more advanced than at the previous examinations. June 24, high protein was discontinued, and June 26, only a trace of albumin was present in the urine. No red blood corpuscles were found after June 24. Fol-

4. In every case the presence of red blood corpuscles was confirmed by at least two other observers.

lowing discharge, urine specimens were examined July 7 and 30 and August 28, and in each instance neither albumin nor red blood corpuscles were found.

Comment.—In this case twenty-one days of high protein diet resulted in a definite increase in the amount of albumin present in the urine; in the appearance of red blood corpuscles which had previously been absent; in a definite advance in the macular changes of the fundus as shown by ophthalmoscopic examination; and in the appearance of definite edema evidenced by pitting of the ankles and increase in weight. The changes in diet had no effect on the blood pressure.

CASE 2.—Male, aged 58, married, lumber scaler. Entered May 22 complaining of shortness of breath and failing vision. The family history and marital history were unimportant.

Previous Illness.—He had measles in childhood but no scarlet fever or tonsillitis. Ever since early youth he had "rheumatism" in his left knee. He has had frequent attacks of frontal headache which have been especially severe in the last two years. For some time he has had discharge from his left ear and the hearing has been completely lost on this side. He is subject to chronic head colds, and during the last two months he has had occasional attacks of epistaxis. For a number of years there has been nocturia, two to four times. No history of pyuria or hematuria was obtained. His ankles have never been swollen. Recently he has had occasional attacks of dizziness. About two years ago his vision became suddenly blurred and he attributed this to some new glasses which he had just gotten, but several changes of glasses failed to improve it. At about the same time he noticed that he was becoming short of breath on slight exertion and there were occasional attacks of palpitation. This condition has very slowly grown worse up to the present time.

On further questioning, an interesting and important dietary history was obtained. For the past thirty-five years he has worked in a lumber camp, and during the entire time has eaten large quantities of meat. He states that he would average about one-half pound of meat three times daily, and gives as an example of his usual diet: Breakfast: pancakes, fried potatoes, half pound of steak. Noon: roast beef, about one-half pound, potatoes and gravy, corn and tomatoes or some other vegetable. Evening: potatoes and all he could eat of some kind of meat, generally from one-half to three-quarters of a pound.

Physical Examination.—On examination, the pupils were normal in contour and reaction. There was marked impairment of hearing in the left ear. Many of the teeth were absent and a number of those remaining were carious. Pyorrhea was marked. The lungs were normal. The left border of the heart was 11.5 cm. to the left of the midsternal line, and the apex beat was best heard and felt in the fifth intercostal space. The first mitral sound was reduplicated but no murmurs were present at the apex or base. A_2 was markedly accentuated. The liver edge was palpable three finger breadths below the rib margin in the nipple line. The spleen was not felt. Tendon reflexes were all normal. The department of otolaryngology reported old left sided otitis media of no clinical importance.

Ophthalmologic examination showed neuroretinitis with some edema of the nerve head and some old retinal hemorrhages. The blood Wassermann was negative. Red blood corpuscles 5,200,000; hemoglobin, 100 per cent. (Talqvist); white blood corpuscles, 8,650. The blood pressure on admission was 200/120. Phenolsulphonephthalein excretion was 15 per cent. in the first hour; 20 per cent. in the second hour. Blood urea nitrogen was 13 mg. per 100 c.c. From the day of admission, May 22, until May 28, he was kept on a salt poor diet

containing about 35 gm. protein, and during this period careful repeated urine examinations were made. A few white blood cells and an occasional cast were found but at no time was albumin present nor were red blood corpuscles found.

May 27 he was given a Mosenthal meal and variation of urine, specific gravity from 1.008 to 1.020 followed. The quantity of night urine was, however, definitely increased. After seven days of low protein diet his blood urea nitrogen had reached the low level of 7.9 mg. per 100 c.c.

Clinical Observation.—Beginning May 29 his protein intake was increased to the maximum. This was 220 gm. protein the first day and 182 gm. the following day. The first day after high meat diet was started (May 30) albu-

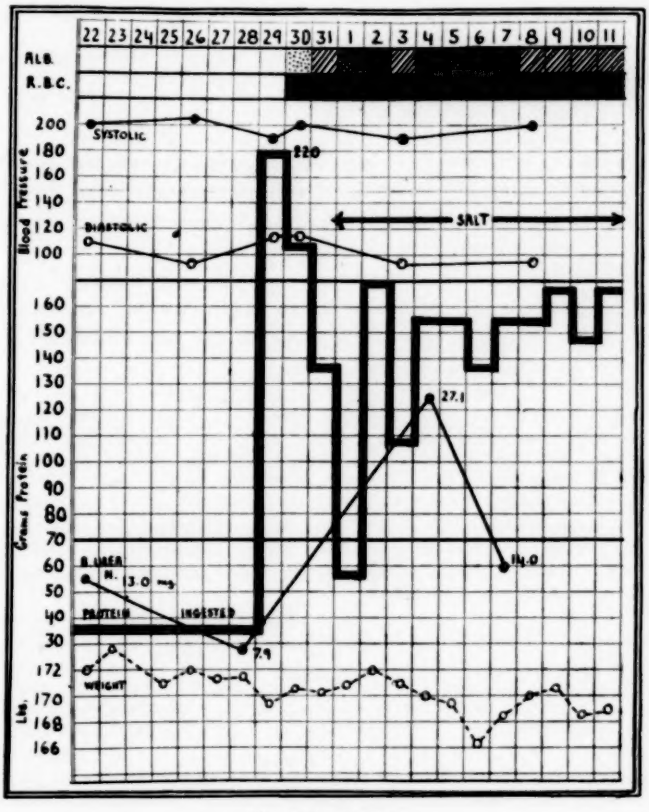

Chart 2.—Case 2.

min was present and a few red blood corpuscles were found. The daily quantity of albumin as determined by the Esbach tube gradually increased from 0.2 gm. per liter to 0.8 gm. per liter on the third day (June 1). On this day salt was added to his diet, and the following day the urine was found to contain 1.7 gm. albumin per liter. High protein diet without salt limitation was continued for ten days (until June 11). During this period there was no increase in weight and no evidence of edema. The blood urea nitrogen

reached a maximum of 27.1 mg. June 4, after which it fell, until June 7 it was 14 mg. The phenolsulphonephthalein excretion showed a striking increase. June 11, the phenolsulphonephthalein elimination for the first hour was 50 per cent. as contrasted with 15 per cent. at the time of admission; and for the second hour it was 25 per cent. as contrasted with 20 per cent. Assuming the first determination to be correct, inasmuch as the technic was the same in both instances, the marked increase in phenolsulphonephthalein elimination would seem to indicate renal irritation. Possibly, the fall noted in blood urea nitrogen may be explained on the same basis. During the period of high protein feeding, daily urinalyses invariably showed from two to six red blood corpuscles to the high power field. June 2, the fourth day after red blood corpuscles were found in the urine, the fundi were reexamined in the department of ophthalmology. They reported as follows:

S. shows a well defined increase of edema in the cup of the right eye, and an increase of hemorrhages both deep and superficial in the left eye. These changes may be construed to be resultant from the same factor or factors causing the original changes noted before.

Comment.—In this case high protein feeding resulted in almost immediate appearance of red blood corpuscles in the urine when they had previously been absent; in definite albuminuria which previously had not been present; in a rise in the blood urea nitrogen, later followed by a fall; in a marked increase in phenolsulphonephthalein elimination, which in conjunction with the secondary fall in blood urea nitrogen is interpreted as possible evidence of renal irritation; and in a distinct increase in retinal hemorrhages.

Case 3.—Scotch drayman, aged 61, married, entered the hospital, August 11, complaining of occipital headaches and dizzy spells. His mother died at 67 of dropsy, and one brother died of Bright's disease. Otherwise the family history is unimportant.

Previous Illness.—He had scarlet fever and diphtheria in early youth but no other serious illness. For many years he has been troubled with headaches and for the past year his vision has been failing. Venereal disease was denied. There have been occasional attacks of sore throat and for the last two years he has had slight asthmatic attacks.

Present Illness.—He dates the onset of the present illness to six months ago at which time he had severe occipital headache accompanied by swelling just above and in front of each ear. Attacks of headache were easily brought on by excitement or exposure to the sun. About two months ago, the pain began to grow worse, and it has steadily progressed since that time, being worse in the morning on arising. There have recently been occasional dizzy spells when he feels as though the blood had "rushed to his head." He has noticed that, at times, large amounts of urine are passed, while at other times the amount is but slight. There has been only occasional nocturia.

Physical Examination.—On examination the teeth were found to be in fair condition, except for marked pyorrhea. The lungs were negative. The heart was slightly enlarged to the left, and at the apex there was a soft blowing systolic murmur faintly transmitted to the axilla. The aortic second sound was accentuated. The radials and brachials were slightly firmer than normal and there was a suggestion of beading. Abdominal examination was negative. No focus of infection could be demonstrated in the nose, throat or ears by the otolaryngology department, and a roentgenogram of the sinuses was normal.

An examination in the department of ophthalmology showed angiopathic retinitis, hyperemia of the nerve head and angiosclerotic changes of both eyes with some choroidal changes in the left eye.

The blood Wassermann was negative, and the hemoglobin, red and white cell counts were all normal. At the time of admission a reducing substance was found in the urine which was otherwise normal, and he was consequently placed on the routine green diet. At no subsequent examination was any reducing substance found. The blood pressure on admission was 195/125. The phenolsulphonephthalein excretion was 10 per cent. in the first hour and 14 per cent. in the second hour. The blood urea nitrogen, determined after eight days of low protein diet, was 11.2 mg. per 100 c.c.

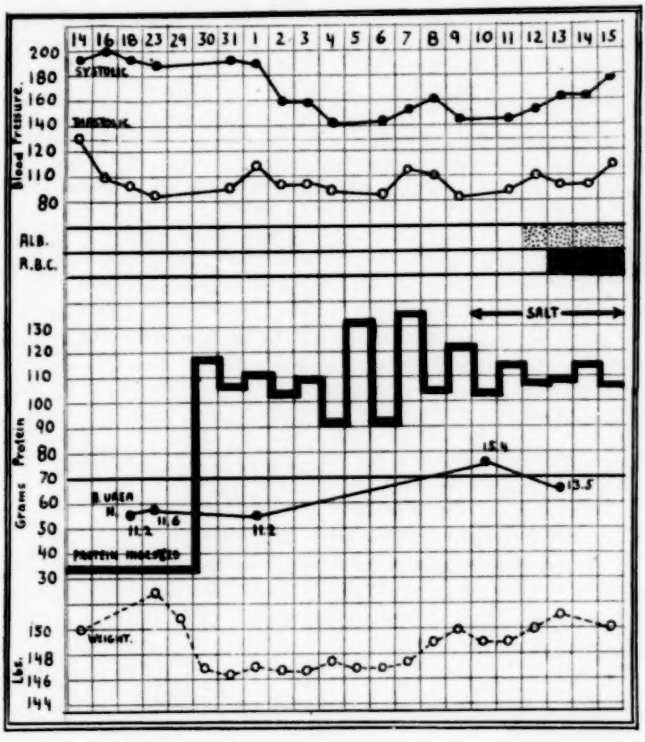

Chart 3.—Case 3.

Clinical Observation.—August 30, after eighteen days of low protein diet, during which time an occasional hyalin cast was the only urinary abnormality found on repeated careful examinations, he was given a high protein diet. It was impossible to induce him to eat as much protein as in either of the preceding cases. After two days of high protein, the urine which had previously been free from albumin contained a distinct trace, which persisted for five days and then disappeared. September 10, after twelve days of forced protein feeding, the blood urea nitrogen was 15.4 mg. per 100 c.c. During the entire time no red blood corpuscles were observed but occasional hyaline casts and a few white blood cells were found each day.

September 11, after thirteen days of high protein, salt was allowed in addition and on the following day, September 12, a trace of albumin was again found in the urine. September 13, the fifteenth day of high protein diet, and after two days of unrestricted salt, from one to two red blood corpuscles to the high power field were found in the urine and on the following day the number of red cells was distinctly increased. September 15, two days after red cells were found, an ophthalmoscopic examination was again made in the department of ophthalmology and the following report returned:

There is considerably more edema of the disk in the right eye, the rings barely showing; the disk is hyperemic; the veins are engorged and the retina has more loss of transparency.

In the left eye the disk is likewise more edematous than at the previous examination and is hyperemic. The veins are engorged. The retina has marked loss of transparency near the disk and in the macular region. Both eyes present a definite increase in edema. No hemorrhages were seen in either eye.

He was discharged September 15, before a phenolsulphonephthalein determination could be repeated. It is interesting, however, to note that the blood urea nitrogen September 13 was 13.5 mg.—distinctly lower than on September 10 before red cells had appeared in the urine.

October 10, a urine specimen submitted for examination showed a trace of albumin but no red blood corpuscles were present.

Comment.—Here, again, prolonged high protein feeding was followed by definite evidence of renal disturbance. Shortly after the initial irritation of high protein feeding, a trace of albumin was found in the urine which had previously been albumin free. After five days of the same diet the urine again became albumin free, but shortly after salt was added to the diet it reappeared. An hypothesis at least worthy of consideration is that subsequent to throwing an added load on the kidneys suddenly, there was albuminuria which disappeared as soon as the kidneys became adjusted to the added task. Again, the further addition of salt to the diet temporarily overtaxed the kidneys with resulting reappearance of albumin.

After continued high protein diet, during the last three days of which salt was allowed, red blood corpuscles appeared in the urine which had previously been free from such cells at each daily examination.

The fundus examinations revealed a moderate but distinct increase in the engorgement and edema of the retina subsequent to the high protein feeding.

No significant change in blood pressure was noted during the period of forced protein diet.

Case 4.—Woman, aged 56; American, housewife, married, entered the hospital, August 26, complaining of pain in the back, shortness of breath, palpitation and nocturia. One sister died of Bright's disease, but otherwise the family history is unimportant.

Previous History.—She had the usual children's diseases with diphtheria at 13, after which she had repeated attacks of sore throat. At 19, following the birth of her first child, she was in bed four or five weeks with scarlet fever complicated by left otitis media. Fifteen years ago she was sick five weeks

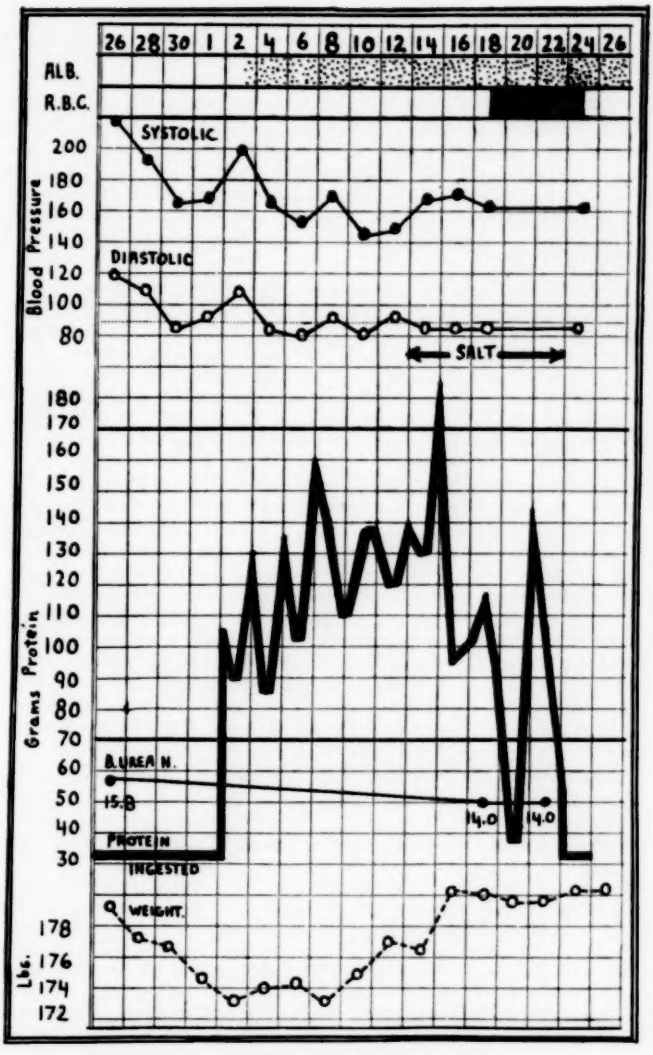

Chart 4.—Case 4.

with what she describes as "congestion of the kidney." At this time there was difficulty in urination and the urine was dark, scant and strong smelling. Her face and ankles were swollen and her mouth very sore. The attack was not associated with any other illness. Four years ago, she had "sciatica." December, 1918, she had influenza and was in bed two weeks after which her throat remained sore for five weeks. December, 1919, she was in bed for three weeks complaining of shortness of breath, tired feeling and pain in the back. During this period she says there were three days during which she passed no urine.

Present Illness.—Her present illness really dates from her trouble fifteen years ago, but since her attack of influenza, although her symptoms have not been markedly worse she has felt more concerned about them. Last March she began to have occasional attacks of sharp pain in the region of the sternum which radiated to the left shoulder. Following an attack she would perspire and feel weak. For several years there has been nocturia twice each night.

Physical Examination.—On examination, the pupils were normal, the tonsils slightly enlarged and the postcervical and submental glands were palpable. There were a few crackles at the base of the right lung, but otherwise the chest was negative. Because of obesity, the heart apex could not be determined very well, but there was no obvious enlargement. The heart sounds were faint, and there was a soft blowing systolic murmur at the apex not well transmitted to the axilla. The aortic second sound was accentuated. The abdomen was negative and except for many varicose veins in the legs, the extremities were negative. There was no edema.

The department of otolaryngology reported small buried tonsils with slight hypertrophic rhinitis. Although a roentgenogram of the head showed some clouding of the accessory sinuses, it was felt that there was no evidence of present active infection. A roentgenogram of the chest showed nothing abnormal, and the heart was reported to be normal in size and shape. The department of ophthalmology reported bilateral angiosclerosis, neuroretinitis, venous engorgement and marked edema. There was also central punctate retinitis.

Her blood Wassermann was negative, and the blood count was normal. The blood pressure on entrance was 220/120. Blood urea nitrogen on admission was 15.8 mg. per 100 c.c. Phenolsulphonephthalein elimination for the first hour was 30 per cent.; for the second hour, 15 per cent. A few white blood cells and occasionally hyalin casts were found in the urine. There were no red blood cells and no albumin was present.

Clinical Observation.—For seven days following admission she was kept in bed on low-protein, salt-free diet. During this time there was a tendency for her blood pressure to fall. September 2, forced high protein feeding was begun. The initiation of high protein feeding made no change in the general downward trend of her blood pressure. September 3 a trace of albumin was found in the urine and this persisted in an amount practically unchanged during her stay in the hospital. September 14, after twelve days of high protein diet, salt was allowed in addition to the high meat, and September 19, after seventeen days of high protein feeding and five days after the addition of salt, rare red blood corpuscles were found in the urine. Red cells were found in the urine in small numbers for four succeeding days until the high protein diet was discontinued. September 25, after two days of low protein diet, there was still a trace of albumin but no red cells were found. During the high protein feeding the level of blood urea nitrogen remained practically constant, being 14 mg. per 100 c.c. September 17 and again September 22. On this last day, the phenolsulphonephthalein elimination was 22 per cent. for the first hour and 24 per cent. for the second hour. Ophthalmoscopic examination made September 23, three days after red cells were found, showed practically the same appearance reported at the first examination.

Comment.—It is seen in this case that an initial hypertension gradually fell regardless of the protein intake. The urine, which had previously been free from albumin, contained a distinct trace on the second day of the high protein diet. Red blood corpuscles appeared in the urine after a long continued period of high protein diet during the

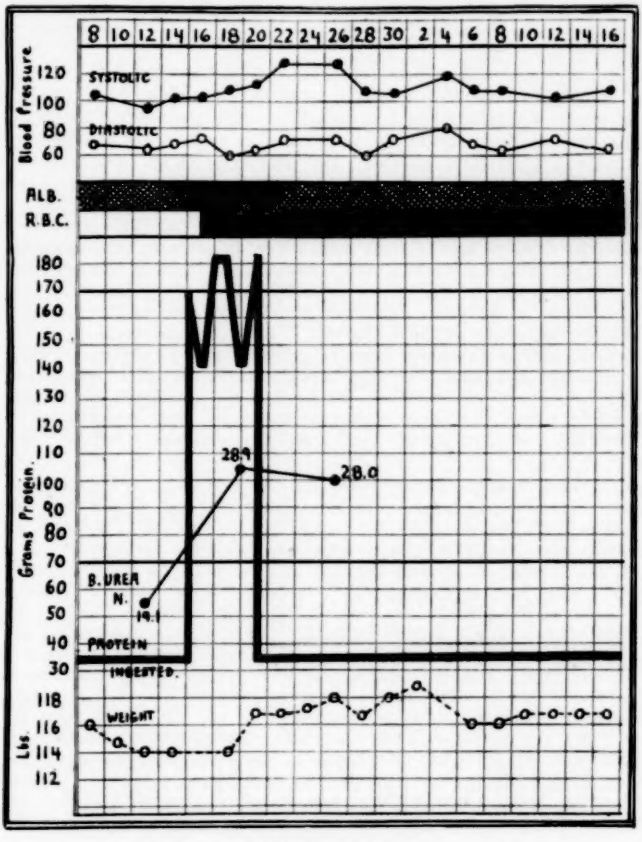

Chart 5.—Case 5.

last days of which there was no salt restriction. The phenolsulphonephthalein output and blood urea nitrogen remained practically constant during the high protein feeding.

The appearance of red blood corpuscles in the urine of these patients after high protein feeding appeared to us so interesting that we were led to study the effect of such diet in undoubted nephritis.

CASE 5.—Male, aged 38, married, entered the hospital June 7, complaining of edema of the face and ankles. The family history was unimportant.

Previous History.—There was no history of scarlet fever or tonsillitis and the past history was negative until four years ago when he had psoriasis. About April, 1920, after a series of roentgen-ray treatments for his psoriasis he noticed that he was becoming edematous. His face was first affected, and then his ankles. The onset was gradual and became progressively worse. He was treated for nephritis in a hospital for three weeks and felt somewhat improved at the time of his discharge. He entered this hospital on the advice of his home physician.

Physical Examination.—On examination, the pupils were found to be normal in contour and reaction. There was marked pyorrhea. The tonsils were enlarged and somewat injected, and there was moderate cervical adenitis. Over the chest, abdomen, knees and elbows there was evidence of psoriatic lesions. The lungs and heart were normal. The liver edge could be felt one finger-breadth below the rib margin in the nipple line. There was no demonstrable edema of the ankles and the tendon reflexes were normal.

The day following admission the department of ophthalmology reported neuroretinitis with edema in both eyes. The department of otolaryngology reported hyperseptic tonsils and nasal obstruction, advising tonsillectomy and submucous resection. Dental films showed a moderate generalized pyorrhea but no evidence of a focus. However, six carious teeth were found by the oral surgeon and immediately removed.

The blood Wassermann was negative. Hemoglobin, 90 per cent. (Talqvist); red blood corpuscles, 4,000,000; white blood corpuscles, 9,400. Blood pressure was 105/70. The urine showed a definite cloud of albumin on heating but not enogh to give a flocculent precipitate and there were a number of white blood corpuscles and occasional hyalin and granular casts but no red blood corpuscles.

Clinical Observation.—On admission he was placed on a low-protein, salt-free diet. The phenolsulphonephthalein elimination was 47 per cent. for the first hour and 18 per cent. for the second hour. June 12, after five days of low protein diet, the blood urea nitrogen was 19.1 mg. per 100 c.c.

June 16 forced high protein feeding was started. On the following day (June 17), after having ingested 170 gm. protein on the preceding day, from three to five red blood corpuscles were found in the urine per high power field. After three days of high protein (June 19) the blood urea nitrogen had risen to 28.9 mg. High protein was continued until June 21, and daily urine examinations invariably showed numbers of red blood cells. The amount of albumin which had previously been too small to give a flocculent precipitate, was markedly increased and determinations made by the Esbach method showed 4 gm. per liter during the high protein period. June 18, the day following the appearance of red blood cells in the urine and three days after the initiation of high protein diet, the eyes were reexamined in the department of ophthalmology and no change was reported. June 21, after five days of high protein, the ophthalmoscopic examination was again repeated. This time an "increase in engorgement and edema" of both eyes was found.

June 26, after he had again been on low-protein salt-poor diet for five days, the albumin in the urine had diminished to 0.5 gm. per liter but red blood cells were still found in the urine. Phenolsulphonephthalein elimination determined at this time was 46 per cent. for the first hour and 26 per cent. for the second hour, while the blood urea nitrogen still remained high, being 28 mg. per 100 c.c.

He remained in the hospital on a low-protein, salt-poor diet until July 19, during which time the albumin content of the urine varied between 0.5 and 1.8 gm. per liter. Red blood cells were found in the urine at every examination. July 3, tonsillectomy was done. July 29, after he had been on a low-

protein, salt-free diet for thirty-eight days, he returned for reexamination and the department of ophthalmology reported "edema of right nerve head slightly less than at previous examination (June 23). No hemorrhages. Edema of left nerve head considerably less than at last examination. No hemorrhages." Urine specimens submitted for examination during the months of August, September and October all showed the presence of a few red blood corpuscles, and the albumin varied between 1.5 and 2 gm. per liter.

Comment.—In this patient the kidney changes may be assumed to be more recent and active, and consequently the added load of the high protein caused more lasting urinary disturbances than were seen in the preceding cases. The albumin content of the urine increased markedly during the period of high protein feeding and decreased again upon return to the low protein diet. Red blood corpuscles in the urine appeared promptly after high protein feeding was begun and were subsequently found at every examination. The blood urea nitrogen was increased and remained at a relatively high level after several

TABLE 1

Case No.	Blood Pressure		Pulse Pressure	2 Hr. Phthalein		Average Protein Eaten, Gm. per Kg. per Day	Number Days Before R. B. C. Found
	Systolic	Diastolic		Before High Protein	After High Protein		
1	250	150	100	20	22	2.7	21
2	200	115	85	35	75	2.8	1
3	165	95	70	24	20*	1.6	14
4	160	90	70	45	46	1.5	17
5	110	60	50	65	68	3.2	1

* Third day of high protein.

days of low protein diet. Following the high protein diet there was an increase in the engorgement and edema of the nerve head which diminished again after a long period of low protein diet. The blood pressure was uninfluenced by high protein feeding.

In two instances patients were studied in whom renal abnormalities were discovered by accident. The blood pressure in each case was normal, and in one (Case 6) the urine examination gave no evidence of disease, while in the other there were a few red cells and occasional casts but no albumin.

CASE 6.—Male, aged 28, physician, married.

Previous History.—He had measles in early childhood and typhoid at 17. He has never had scarlet fever. In August, 1919, he had a severe attack of tonsillitis at which time *Streptococcus hemolyticus* was isolated from his throat. February, 1920, there was a second severe attack of tonsillitis, and in March, 1920, tonsillectomy was performed.

Physical Examination.—Physical examination showed nothing abnormal. Blood pressure was 125/80. The urine specific gravity was 1.018 and there were no white or red blood cells, casts or albumin present. Phenolsulphonephthalein elimination was distinctly low, being 26 per cent. for the first hour and 21 per cent. for the second hour.

Clinical Observation.—October 1, high protein feeding was begun. The following morning as many as two red blood corpuscles were found per high power field, together with an occasional white blood cell and one granular cast. A questionable trace of albumin was present in the urine. On the following day, red cells were present in about the same numbers, and there was a distinct trace of albumin. After the second day, the high meat diet was discontinued, but red cells were still found in the urine on the following day, October 4. Subsequently, no red blood corpuscles and no casts were found at any of the urine examinations which were made daily until October 22. A trace of albumin was present until October 6. On the second day of the high meat diet, the phenolsulphonephthalein excretion was 16 per cent. for the first hour and 22 per cent. for the second hour, while the blood urea nitrogen was 15.8 mg. per 100 c.c. September 11 the phenolsulphonephthalein excretion was 19 per cent. for the first hour and 20 per cent. for the second hour, while September 22 it was 23 per cent. in the first hour and 22 per cent. in the second hour. An ophthalmoscopic examination after red cells appeared showed no abnormalities in the fundus.

Comment.—Certainly the phthalein elimination in this subject was unusually low at each determination, but previous to the meat feeding there was no other indication of kidney abnormality. The blood chemistry was not done at this time. However, January 28, on his normal diet the total nitrogen of the blood was 35.4 mg.; urea nitrogen, 17.3 mg.; preformed creatinin, 1.8 mg.; and uric acid, 4.75 mg. per 100 c.c. In view of the diminished phenolsulphonephthalein excretion in this case, together with the slightly increased blood uric acid, the conclusion is certainly justified that we are dealing with an early nephropathy. Promptly after forced meat diet, red cells and a trace of albumin appeared in the urine and phenolsulphonephthalein elimination, which was already low, fell from 26 to 16 per cent. for the first hour.

Case 7.—Male, physician, aged 38. There was no knowledge of kidney disturbance of any kind and this case was studied as one of the normal control group reported in the second part of this paper.

Previous History.—During infancy and childhood there were repeated attacks of croup and head colds. At the age of 7 and 14 tonsillectomies were performed, and at 21 he had an attack of double quinsy after which tonsillectomy was again done. In 1901, he had pneumonia with good recovery. In 1910, there was a severe antrum infection and a drainage was attempted by drilling into the sinuses. He has not had scarlet fever.

Physical Examination.—The blood pressure was 135/90 and no evident abnormalities were present on physical examination.

The urine showed no albumin, but there was a trace of nucleo-albumin. There were a few hyalin and granular casts, and from two to four red blood corpuscles were present in each high power field. Phenolsulphonephthalein elimination was 35 per cent. for the first hour and 16 per cent. for the second hour. Blood nitrogen and preformed creatinin were normal but the blood uric acid was slightly increased, being 4.6 mg. per 100 c.c.

Clinical Observation.—Following these determinations large steaks were eaten at the noon and evening meals. A definite trace of albumin was present in the urine during the following day but was again absent during the next succeeding day. Red blood corpuscles and hyalin and granular casts were present at every examination. On the day following the meat meals, the phenolsulphonephthalein elimination was 48 per cent. for the first hour and

14 per cent. for the second hour as compared with the original determination of 35 per cent. and 16 per cent. for the first and second hours, respectively. The preformed creatinin of the blood remained practically unchanged, but the total nitrogen increased from 30.6 mg. to 45.7 mg. per 100 c.c., and the uric acid from 4.6 to 5.1 mg. per 100 c.c. January 15, two weeks after the original examination, and again January 26, urine specimens were examined and found to be albumin free, but there were from two to four red blood corpuscles to a high power field and occasional granular and hyalin casts.

The feeding of high protein as a test for the presence of nephritis in cases of so called "essential hypertension" is inadequate to answer the original question, as will appear in Part 2, where it will be shown that it produced abnormalities in the urine of normal subjects. The work has, however brought to light information of great interest.

PART 2

RENAL IRRITATION IN NORMAL YOUNG MEN AFTER HIGH PROTEIN FEEDING

Since high protein feeding so regularly has been followed by the appearance of red blood corpuscles in the urine in the group of individuals described in Part 1, and since, in a few instances, a very short period of such feeding had this effect on kidneys which in the present state of our knowledge showed but slight evidence of damage, we asked ourselves the question whether even the normal kidney might not show evidence of irritation when forced to rid the body of the waste products resulting from a very brief period of protein excess.

As a preliminary experiment, one of us (T. S.) ate at 6:00 p. m. an enormous steak (about one pound) with a few potatoes and one cup of coffee. Urine passed at 8:00 p. m. was acid, specific gravity, 1.020, and free from albumin, white blood cells and casts, but contained from two to four red blood corpuscles per high power field. The blood urea nitrogen determined at 9:10 p. m. was 20.7 mg. Subjectively, there was a slight headache and the sensation of having merely over-eaten. During the twenty-four hours beginning at 8:00 a. m. the day following the excessive meat meal there was a total excretion of 13.39 gm. nitrogen in the urine. In the morning urine specimen there was no albumin, white blood cells or casts and no red blood cells could be found after a long and careful search. At 8:00 a. m. the blood urea nitrogen level was still slightly high—18.6 mg.

The effect of two high protein meals on normal men was next studied, medical students being used as subjects. On the day preceding the meat meals the total nitrogen, urea nitrogen, preformed creatinin and uric acid content of the blood were determined by the

TABLE 2.—Showing the Effect of Two Forced Meat Meals in Normal Young Men

Name	Day	Hour	Urine														Phthalein		Blood			
			Amount	Reaction	Specific Gravity	Albumin	Casts	Red Blood Corpuscles	White Blood Corpuscles	Total Nitrogen	Urea Nitrogen	Ammonia Nitrogen	Uric Acid	Creatinin	Chlorids		1st Hour	2d Hour	Total Nitrogen	Urea Nitrogen	Preformed Creatinin	Uric Acid
															Per Cent.	Total						
L. E. H. aet. 24	Before meat...	.....	1,642	Ac.	1.019	0	0	0	++	11.75	7.52	0.82	0.55	1.05	0.80	13.10	50	16	24.1	14.7	1.98	3.57
	Meat day.....	5:00 p. m.	.....	Ac.	1.026	0	0	+	++													
		7:00 p. m.	....	Ac.	1.023	0	0	+	++													
		11:00 p. m.	.....	Ac.	1.023	0	0	+	++													
		Night	1,729*	Ac.	1.019	0	0	0	+	18.66*	12.38*	0.69*	0.73*	2.07*	0.93*	16.08*						
	After meat....	.....	1,399	Ac.	1.025	0	0	0	±	21.96	11.75	0.87	0.56	2.02	0.96	13.40	62	?	58.2	32.4	2.23	2.52
Sl. aet. 31	Before meat...	.....	1,825	Ac.	1.023	0	0	0	0	11.09	5.03	0.40	0.32	1.50	0.85	15.5	47	10	33.9	15.6	1.74	2.39
	Meat day.....	5:00 p. m.	.....	Ac.	1.027	0	0	+	±													
		11:00 p. m.	.....	Ac.	1.020	0	0	+	+													
		Night	1,460*	Ac.	1.022	0	0	0	+	13.57*	7.00*	0.37*	0.32*	1.21*	0.57*	8.3*						
	After meat....	.....	1,540	Ac.	1.023	0	0	+	++	27.45	22.23	0.52	0.35	2.07	0.84	12.9	47	13	48.9	21.4	2.01	4.02
Elz. aet. 24	Before meat...	.....	1,810	N.	1.019	0	0	0	0	8.56	5.54	0.34	0.20	1.63	0.45	.....	52	16	22.9	13.0	1.66	1.87
	Meat day.....	5:00 p. m.	.....	N.	1.020	0	0	0	0													
		11:00 p. m.	.....	N.	1.018	0	0	+	±													
		Night	2,340*	N.	1.016	0	0	0	0	20.61*	14.32*	0.60*	0.38*	1.63*	0.44*							
	After meat....	.....	2,005	Ac.	1.022	0	0	0	0	19.64	13.05	0.50	0.18	2.30	0.81	.....	32	24	40.5	21.2	2.04	4.75
Ch. aet. 30	Before meat...	.....	1,770	Ac.	1.017	0	0	0	+	14.22	12.92	0.90	0.87	2.08	0.64	11.3	56	12	40.8	19.8	1.50	1.40
	Meat day.....	5:00 p. m.	.....	N.	1.012	0	0	+	+													
		11:00 p. m.	.....	Ac.	1.028	0	0	+	+													
		Night	2,280*	N.	1.014	0	0	±	+	22.11*	13.68*	0.82*	0.65*	2.31*	0.47*	10.2*						
	After meat....	.....	1,500	Ac.	1.021	0	0	+	+	14.70	10.20	0.75	0.45	2.02	0.36	5.4	50	15	51.9	24.0	2.10	3.40

* Twenty-four hour amount

Folin-Wu method. Before the test the average amount of these various constituents was:

Total N	30.4 mg. per 100 c.c.
Urea N	15.7 mg. per 100 c.c.
Preformed creatinin	1.74 mg. per 100 c.c.
Uric acid	3.67 mg. per c.c.

Phenolsulphonephthalein elimination averaged 48 per cent. for the first hour and 14 per cent. for the second hour. Quantitative determinations of the total nitrogen, urea nitrogen, ammonia nitrogen, uric acid, creatinin and chlorids of the urine were made in twenty-four hour periods preceding on the day of the meat meals and on the day following meat. These results are recorded in Table 2.

At noon and again at 6:00 p. m. of the meat day each subject ate a steak averaging about one and one-half pounds in weight. The urine passed between noon and 6:00 p. m., that passed between 6:00 p. m. and 11:00 p. m., and that passed between 11:00 p. m. and 8:00 p. m. was collected as separate specimens. Each specimen was tested for albumin and the sediment examined. Similar tests were made with the twenty-four hour urine preceding and following the meat diet. For quantitative determinations all the urine passed during the twenty-four hour period of the meat day was mixed.

At 8:00 a. m. on the day following the meat diet, blood analyses were made just as in the preliminary period. The average amounts found on this determination were:

Total N	48.8 mg. per 100 c.c.
Urea N	24.7 mg. per 100 c.c.
Preformed creatinin	2.12 mg. per 100 c.c.
Uric acid	3.67 mg. per 100 c.c.

Consequently, on the morning following meat feeding there was an increase in the average total nitrogen, urea nitrogen preformed creatinin and uric acid of 63.8, 57.3, 21.8 and 59.5 per cent., respectively.

In no instance were red blood cells found in the urine preceding the meat meals. In every case red blood cells were present following the meat feeding. In no instance was albumin found at any examination.

It is evident, therefore, that protein excess for a period as short as one or two meals is sufficient to cause the appearance of red blood corpuscles in the urine of healthy young men.

DISCUSSION AND SUMMARY

Forced high protein feeding in four cases of hypertension in which urinary evidence of kidney disturbance was slight or absent resulted in each case in the appearance of red blood cells in the urine. On return to low protein diet, the red cells soon disappeared. In three cases, albumin was found after the meat diet, although previously none was

present. In one case, albumin originally present as a trace was markedly increased following meat feeding. In three of the four cases a definite increase in fundus changes was noted following the meat diet. The one case of this group (Case 4) in which no increase in fundus changes was seen following meat presented originally the fewest signs of kidney abnormality. It is interesting that in one instance following the added load of high protein diet there was a prompt albuminuria which quickly disappeared. However, the addition of salt, which may be regarded as further increasing the work of the kidney, resulted in the reappearance of albumin followed shortly after by the appearance of red cells in the urine. In one patient (Case 5) the history and urine findings pointed to a more recently active nephritis. Albumin was present as a heavy cloud in the urine and there were a number of casts. The blood pressure was normal. After high protein feeding, red blood corpuscles which had previously been absent promptly appeared in the urine of this patient, and the amount of albumin was greatly increased. Whereas, in all other cases the red blood cells disappeared promptly after a return to low protein diet, in this case red blood cells were found at every subsequent examination. An increase in the engorgement and edema of the nerve head was also noted following the forced protein, while after a few days of low protein diet this edema and engorgement had distinctly decreased.

Neither protein restriction nor high protein feeding had any influence on the blood pressure in any of these cases, and such a failure of protein diet to influence blood pressure agrees with the observation of Mosenthal.[5]

Two cases of the series (Cases 6 and 7) were especially interesting inasmuch as previous to this study there had been no knowledge of kidney impairment. In both cases preceding the test albumin was absent from the urine, while following the high protein a distinct trace was found, which again disappeared after return to normal diet. In one of the cases (Case 7) inasmuch as red cells were found preceding the test, a slight increase in numbers would fail to give information of value, but in the other case (Case 6) red cells which were absent before the feeding were found after the high meat feeding and promptly disappeared on return to normal diet.

Forced meat feeding for two successive meals was invariably sufficient to cause the appearance of red blood corpuscles in the urine of five normal young men. On return to a normal diet, the red cells promptly disappeared. In no case was there detectable albuminuria. The nonprotein nitrogen constituents of the blood on the morning following the meat meals were much higher than before the test. Pre-

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formed creatinin was increased least, being 21.8 per cent. higher than on the day preceding the test, while urea nitrogen and uric acid were increased 57.3 and 59.5 per cent., respectively.

By consulting Table 2 it will be seen that Cases 5 and 2 with a daily protein intake of 3.2 and 2.8 gm. per kilo, developed red cells in the urine on the second day, while in Case 1, although the daily protein ingested was 2.7 gm. per kilo red cells did not appear for twenty-one days. It is suggestive that this last case showed the most evidence of kidney sclerosis of the series, the phenolsulphonephthalein elimination being lowest and the blood pressure and pulse pressure highest. It seems not improbable that the delay in the appearance of red cells here may be due, in part, at least, to a loss in flexibility of the kidney capillaries. It is worth while again calling attention to the fact that the phenolsulphonephthalein elimination for two hours increased in Case 2 from 35 per cent. before meat feeding to 75 per cent. after red cells had appeared, and in Case 5 from 65 to 72 per cent., while, on the other hand, in Case 1 the phenolsulphonephthalein for two hours was less than 20 per cent.

Assuming the truth of our assumption that high protein diet acts as a kidney irritant, it would be expected that in cases in the acute or subacute stage of nephritic involvement it would cause a more marked and persistent disturbance. That this assumption has support is evidenced by Case 5 of this series in which following meat the albumin output was greatly increased and the red cells persisted in the urine for three months during which time the patient was under observation, instead of promptly disappearing upon return to a normal diet. Further evidence pointing to an acute exacerbation of kidney disturbance in recently damaged kidneys after a high meat diet will be discussed in a subsequent paper.

1. Forced high protein feeding in the presence of kidney damage resulted in the appearance of red blood corpuscles in the urine, and in the appearance of albuminuria or in an increase of a pre-existent albuminuria.

2. Forced high protein feeding invariably resulted in the appearance of red blood corpuscles in the urine of normal men.

3. In some of the cases receiving high protein diet there was a definite increase in the edema and macular changes of the fundus following the meat.

4. High protein diet over a short period had no effect on the blood pressure.

CONCLUSION

Evidence is presented to show that high protein diet in man is a renal irritant.

II. THE EFFECT OF CYANIDS AND OF ORGANIC OXIDIZING AGENTS ON THE LIVER INJURY CAUSED BY CHLOROFORM *

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The series of experiments here recorded were undertaken with the hope of throwing some light on the etiology of chloroform liver necrosis. Should this liver injury be caused by a reduction of tissue oxidation, it is conceivable that the cyanids, which apparently act by preventing oxidation, might increase the damage to be expected from chloroform if the two drugs were given simultaneously. On the other hand, iodozo- and iodoxy-benzoic acids and their sodium salts, which readily give up oxygen to the tissues, might lessen the expected injury.[1]

We have already reported a few experiments in which potassium cyanid was administered intravenously, either alone or in conjunction with prolonged chloroform anesthesia.[2] Although large doses of the drug itself produce an extensive fatty alteration in the liver parenchyma, smaller amounts, given during the administration of chloroform, affect the liver changes produced by the anesthetic very little, if at all.

Experimental work by Verworn [3] tends to show that the depression caused by narcotics is really an asphyxiation. His hypothetical suggestion is that the oxygen carriers are unable to supply oxygen to the tissues, perhaps because the enzymes are of a lipoidal nature with consequent affinity for the usual anesthetics. Burge [4] reports that the oxidative enzyme catalase is greatly reduced by anesthetics, most pronouncedly by chloroform. This might be considered to support the views of Verworn. However, both the method [5] and the conclusions of Burge have frequently been questioned.[6]

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† University of California Fellowship.

1. We are indebted to Professor Loevenhart of the University of Wisconsin for liberal supplies of iodozo- and iodoxy-benzoic acids, also for valuable criticisms and suggestions relative to the experiments.

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Buckmaster [7] has shown that at the point of anesthesia with chloroform, from 64 to 71 per cent. of the drug is held by the red corpuscles; after inhalation of 2 per cent. chloroform for three-quarters of an hour, 98.5 per cent. is found in the erythrocytes. He also demonstrated that in the first three minutes of anesthesia lung ventilation is reduced from 30 to 80 per cent.; he considered, however, that the reduction of oxygen in the blood is not due to the latter cause but to the effect of the chloroform on the corpuscles (oxygen carriers).

Graham [8] has stated that chloroform is one of a group of substances whose effect on organs is like that of asphyxiation. He surmised that these drugs dissociate in the body, yielding a molecule with bivalent or unsaturated carbon which eagerly seizes oxygen. However, in a recent article [9] he has dismissed this theory. Buckmaster [7] has reported that he could not detect the formation of carbon monoxid from chloroform in the body.

Wells [10] has suggested that chloroform may first unite with the cell lipoids, perhaps physically, then poison the protoplasm by interfering with oxidative or synthetic functions.

The standard textbooks of pharmacology discuss the cyanids quite fully; Evans' [11] article on "Cyanid Anoxemia" is a good recent contribution. Work seems to show that the cyanids prevent oxidations in the tissues themselves, whether by action on protoplasm directly or by inhibition or destruction of intermediary enzymes is not quite clear. The oxygen carrying power of the blood is not impaired.

Loevenhart and his co-workers have for many years been interested in physiologic oxidations. They have been able to produce central necrosis in rabbits' livers by suboxidation, the animals being left in an atmosphere of low oxygen tension for several days at a time.[12] Loevenhart and Grove,[13] also Arkin [14] have studied the preparation of iodoxy-

7. Buckmaster, G. A.: Proc. Roy. Soc. Med., Lond., Sect. Anesth. **11**:15, 1918.

8. Graham, E. A.: J. Exper. M. **15**:307, 1912; J. A. M. A. **69**:1666 (Nov. 17) 1917.

9. Graham, E. A.: Arch. Int. Med. **25**:575 (June) 1920.

10. Wells, H. G.: J. A. M. A. **46**:341 (Jan. 29) 1906; Arch. Int. Med. **1**: 589 (April) 1908; Chemical Pathology, Philadelphia, W. B. Saunders Co., 1918, Ed. 3.

11. Evans, C. L.: J. Physiol. **53**:17, 1919.

12. Martin, G. H.; Bunting, C. H., and Loevenhart, A. S.: J. Pharmacol. & Exper. Therap. **8**:112, 1916.

13. Loevenhart, A. S., and Grove, W. E.: J. Pharmacol. & Exper. Therap. **1**:289, 1909.

14. Arkin, A.: J. Infect. Dis. **13**:408, 1913.

15. Amberg, S., and Knox, J. H. M.: J. Pharmacol. & Exper. Therap. **3**: 223, 1911. Amberg, S.: Ztschr. f. d. ges. exper. med. **2**:19, 1913. Amberg, S.; Loevenhart, A. S., and McClure, W. B.: J. Pharmacol. & Exper. Therap. **10**: 209, 1917.

16. Loevenhart, A. S., and Grove, W. E.: J. Pharmacol. & Exper. Therap. **3**:101, 1911. Grove, W. E., and Loevenhart, A. S.: J. Pharmacol. & Exper. Therap. **3**:131, 1911.

benzoic and iodozo-benzoic acids. Amberg,[15] Loevenhart,[16] Arkin,[17] and others have studied the effect of these acids and their sodium salts on inflammatory reactions, and the antagonism to cyanids. It has been found that cyanids intensify and organic oxidizing agents diminish inflammatory processes, such as the mustard oil reaction and the intracutaneous reaction in serum sensitization; these results seem to be due to the effect on bodily oxidations and reductions. Arkin [18] tested the bactericidal property of sodium iodoxy-benzoate and found a definite relationship between this and its oxidizing power. Arkin and Fink [19] also studied the effect of this sodium salt on catalase in the blood and tissues; they found that catalase normally varies immensely and that the values after administration of iodoxy-benzoate fell within normal limits. Loevenhart and associates [20] have recommended the therapeutic use of sodium cyanid as a respiratory stimulant. Loevenhart and Eyster [21] found that iodozo- and iodoxy-benzoates were unable to replace molecular oxygen for the maintenance of activity in the isolated mammalian heart. These oxidizing agents were reduced, however, and caused the heart to develop rigor, probably because of the oxidation of some substance in its musculature. Iodozo- and iodoxy-benzoates apparently transfer their available oxygen directly to the substance to be oxidized, without an intermediate liberation of free oxygen; certain oxidizing enzymes seem to facilitate the transfer; in certain peroxidase reactions the organic oxidizing agents act in a manner comparable to hydrogen peroxid.[16]

METHODS

Dogs have been used as experimental animals. Rats were tried, but even the controls differed so much in reaction that the experiments are of little value; these individual variations were probably due, in part, to nutritional differences and the difficulty of imposing a fasting period to reduce the animals to a starvation base line; moreover, the immediate mortality from chloroform injection was very high. Dogs have always been starved three or four days to eliminate the effect of diet on the chloroform injury.

Squibbs' chloroform has been used for both anesthesia and injections. Chloroform anesthesia has been light; the drug was administered by the drop method. When given subcutaneously, chloroform was mixed with twice its volume of liquid petrolatum; syringe plungers

17. Arkin, A.: J. Infect. Dis. **16**:349, 1915.
18. Arkin, A.: J. Pharmacol. & Exper. Therap. **3**:145, 1911.
19. Arkin, A., and Fink, E. B.: J. Infect. Dis. **22**:515, 1918.
20. Loevenhart, A. S.; Lorenz, W. F.; Martin, H. G., and Malone, J. Y.: Arch. Int. Med. **21**:109 (Jan.) 1918.
21. Loevenhart, A. S., and Eyster, J. A. E.: J. Pharmacol. & Exper. Therap. **5**:21, 1913.

were removed and the substances measured directly into the barrels, first, the oil then the chloroform from a 1 c.c. pipet calibrated to hundredths; the mixtures were injected immediately after measurement. Dogs were under light ether anesthesia during the injection of chloroform and other substances. The amount of chloroform injected has not been of itself sufficient to produce unconsciousness, or even instability of equilibrium in many cases.

A liver injury produced by either method may be repeated accurately under the same experimental conditions if an intervening recovery period of three or four weeks is allowed. This possibility has been discussed in a previous communication [22] and subsequent experiments have verified our belief.

Specimens of iodozo- and iodoxy-benzoic acids were furnished by Dr. Loevenhart. His directions for preparing solutions for intravenous injections were briefly: Dissolve 1.32 gm. iodozo-benzoic acid, or 1.4 gm. iodoxy-zenzoic acid, in 20 c.c. water and 10 c.c. normal sodium hydroxid and dilute to 100 c.c. with water; solutions are to be prepared fresh just before using (intravenously). We never had occasion to use 100 c.c. at one time, hence we made up smaller amounts proportionately and by similar steps. To facilitate giving over an extended period of anesthesia these amounts were further diluted with physiologic sodium chlorid solution. When given subcutaneously, iodoxy-benzoic acid was used in relatively large amounts in small volumes of alkaline fluid. Since sodium hydroxid was the solvent, the drug actually employed was sodium iodoxy-benzoate or iodozo-benzoate, as the case might be; however, in the tables and protocols the record gives only the amount of acid corresponding to the volume of solution used. For instance, if 0.2 gm. acid was dissolved in 200 c.c. alkaline fluid, and 150 c.c. of this solution was used, the records show 0.15 gm. acid administered. Iodoxy-benzoate solution given subcutaneously was diluted with 10 per cent. acacia solution; iodozo-benzoic acid was given subcutaneously as a suspension in 10 per cent. acacia solution.

The potassium cyanid employed was a Braun-Knecht-Heimann product, from 98 to 99 per cent. pure; the sodium cyanid was supposed to be chemically pure. The cyanids were dissolved in physiologic sodium chlorid solution immediately before use.

Large amounts of fluid given intravenously have been administered by gravity method, from a funnel through a rubber tube with a glass section near the vein to act as a window, into the external jugular vein through an ordinary large syringe needle; rapidity of flow has been controlled with a screw pinch-cock.

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22. Davis, N. C., and Whipple, G. H.: Arch. Int. Med. **23**:612 (May) 1919.

In case the dogs survived, it has been our routine to operate two days after the administration of chloroform and remove a small piece of liver, either by ligating and snipping off the tip of a pointed lobe, or by inserting a mattress suture in the edge of a larger lobe and excising a wedge of tissue from the area thus deprived of blood. Operations have been performed always under ether anesthesia, and with aseptic precautions. We consider that the best time to estimate tissue injury is on the second day following the injection of the chloroform, since the necrosis is then usually well demarcated and debris is not yet in process of removal. Specimens are fixed in 10 per cent. formaldehyd solution and divided for (1) frozen sections (fat stains, etc.), and (2) paraffin embedding with subsequent hematoxylin and eosin staining. Estimates of necrosis and fatty degeneration are always based on microscopic examination of the paraffin sections.

The fact that we consider one small specimen of liver tissue as representative of the whole may appear unwarranted. Dowler and Mottram [23] studied the fat content of different parts of the liver after injection of fat into the hepatic artery, glycogen after a heavy meal of cane sugar, and fatty acids during fasting periods, and concluded that the distribution of these substances is irregular and unpredictable; however, they admit that the liver of a fasting dog gives the nearest approach to even distribution. Sérége [24] in determining urea and glycogen, and Bartlett, Corper and Long [25] in studying the distribution in the liver of fat injected in the portal vein found considerable differences between the lobes as a whole, but intralobular uniformity. Differences of distribution of these various substances have been correlated with differences in blood supply, i.e., the blood from various portal tributaries does not thoroughly mix, hence is distributed differently. On the other hand, Brissaud and Bauer,[26] also Gilbert and Villaret [27] found an equal distribution of injected gelatin throughout the liver.

When dogs have died of chloroform liver injury we have always taken sections from various parts of the liver, representing several lobes. Ignoring the single layer of liver lobules immediately beneath the capsule (which are usually severely injured), these sections have invariably shown the same picture. Consequently, we have always felt justified in basing our estimations on a biopsy specimen from one lobe only.

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23. Dowler, V. B., and Mottram, V. H.: J. Physiol. **52**:166, 1918.
24. Sérége: Compt. rend. Soc. d. Biol. **54**:200, 1902; **56**:597, 600, 1904; **58**:519, 1905. (Cited by Dowler.)
25. Bartlett, F. K.; Corper, H. J., and Long, E. R.: Am. J. Physiol. **35**: 36, 1914.
26. Brissaud and Bauer: J. d. l'Anat. **45**:1, 1909.
27. Gilbert, A., and Villaret, M.: Arch. d. méd. exper. **21**:373, 1909.

EXPERIMENTAL OBSERVATIONS

Table 1 summarizes the essential details of experiments in which organic oxidizing agents were given intravenously during chloroform anesthesia. A representative protocol follows; it is scarcely necessary to add protocols for all the dogs.

EXPERIMENT 2.—*Control. Simple Starvation and Chloroform Anesthesia.* Dog 19-39, female Airdale.

Oct. 8, 1918: Weight, 26.1 pounds. Isolated before daily feeding; in good condition. Fasting begun.

October 9: Weight, 25.8 pounds; October 10: weight, 24.8 pounds. No food.

October 11: Weight, 24.5 pounds. Active and healthy. Chloroform anesthesia for one and a quarter hours (from 5:50 to 7:05 p. m.).

October 12: Weight, 23.1 pounds. Bright and active.

October 13: Weight, 22.9 pounds. Bright and active.

October 14: Weight, 22.8 pounds. Piece of liver removed at 9:30 a. m. Sections show approximately 60 per cent. necrosis (beginning resolution); fat (scattered). Mixed diet.

Chloroform Anesthesia Plus Sodium Iodoxy-Benzoate Intravenously.—Dog 19-39, female Airdale.

March 5, 1919: Weight, 33.8 pounds. Isolated before daily feeding; fasting begun; has completely recovered from previous experiments; in excellent condition.

March 6 and 7: No food.

March 8: Weight, 31.5 pounds. Active and healthy. Chloroform anesthesia for one and a quarter hours (from 2:45 to 4 p. m.). Intermittently during this period 0.21 gm. iodoxy-benzoic acid (freshly prepared in 15 c.c. alkaline solution, then diluted to 200 c.c. with physiologic sodium chlorid solution) was given intravenously. No ill effects of moment were observed either during or following the injection.

March 9: Active. Mixed food.

March 10: Active. Piece of liver removed at 1:30 p. m. Considerable bleeding occurred. Milk and mixed diet. Sections show approximately 60 per cent. necrosis with a scattering of fat in the dead tissue.

These experiments seem to indicate that iodoxy- and iodozo-benzoic acids have little, if any, protective value against liver necrosis when given intravenously. This may be due to the small amounts of the drugs so given. The intravenous solutions were administered slowly and fairly uniformly throughout anesthesia, intermittently (as in Experiment 2), or steadily during the first forty-five or sixty minutes of anesthesia and none the last few minutes. In Experiment 1 some difficulty was encountered due to apnea during anesthesia, but the dog roused somewhat afterward; death, probably from the iodoxy-benzoate, occurred too early to determine accurately the extent of liver injury; there seemed to be some central disintegration, however. In Experiment 4 there appeared to be a definite lessening of necrosis after injection of iodozo-benzoate; in this case intravenous injection was continued steadily during the first hour of anesthesia; the liver showed one-quarter to one-third necrosis with extensive vacuolization and fat up to one-half; the uninjured lobule peripheries showed considerable

TABLE 1.—Chloroform Inhalation Plus Organic Oxidizing Agents Intravenously

Experiment Number	Dog Number	Date, 1919	Weight, Lbs.	Fasting Period, Days	Chloroform Anesthesia, Hours	Organic Oxidizing Agent	Liver Injury		Remarks
							Oxidizer Plus Chloroform	Control Chloroform	
1	19-30	Feb. 12	18.6	4	1¼	0.21 gm. iodoxybenzoic acid	?	60% necrosis	Found dead next morning; liver shows some central disintegration, necrosis not determinable; viscera congested
2	19-39	Mar. 8	31.5	4	1¼	0.21 gm. iodoxybenzoic acid	60% necrosis	60% necrosis	
3	19-74 (a)	Feb. 25	13.6	4	1¼	0.14 gm. iodoxybenzoic acid	50% necrosis	50% necrosis	
4	19-74 (b)	Apr. 15	13.8	4	1¼	0.25 gm. iodozobenzoic acid	25% necrosis	50% necrosis	Glycogen appears in liver lobule peripheries, suggesting dog fed by mistake during starvation period
5	19-28	May 6	19.1	4	1¼	0.24 gm. iodozobenzoic acid	50% necrosis	50% necrosis	
6	19-135	May 24	46.5	4	1¼	0.35 gm. iodozobenzoic acid	60% necrosis	.....	Operation two days following chloroform; found dead on sixth day following operation; intense jaundice; hemorrhages in viscera; slight removal of liver debris

glycogen. This glycogen content leads to the question whether or not the dog received food by mistake during the preliminary period of supposed fasting. This storage might have occurred after chloroforming and before operation, but more likely it took place before the administration of chloroform. Glycogen per se may have no protective value against chloroform, but its presence is certainly somewhat of a gage of carbohydrate assimilation, which for some reason is protective. A smaller amount of iodoxy-benzoate had no protective value for this same dog (Experiment 3). Unfortunately, there is no control on the same animal in Experiment 6, but judging from the injuries sustained by the other dogs recorded in the same table, there appears to have been no protection from the amount of iodozo-benzoic acid given.

To summarize Table 1, there seems to have been no protection against chloroform injury from intravenous administration of iodozo- and iodoxy-benzoates in five of six experiments; there seems to have been protection in one case from iodozo-benzoate, but this protection may very well have been from food given by mistake, and not from the drug.

Table 2 summarizes briefly the experiments in which chloroform was given subcutaneously with or without organic oxidizing agents and more ample summaries of certain experiments follow.

EXPERIMENT 13.—Dog 20-17, young, black mongrel, female.

Sept. 26, 1919: Weight, 18.9 pounds. Isolated before daily feeding; healthy and active; fasting begun.

September 27 and 28: No food.

September 29: Weight, 17.2 pounds (7.8 kilos). Active. Gave subcutaneously 1.17 c.c. chloroform (0.15 c.c. per kilo) plus 2.4 c.c. liquid petrolatum; temporary ether anesthesia.

September 30: Bright and active.

October 1: Weight, 16.5 pounds. Removed piece of liver at 2 p. m. Sections show about 35 per cent. necrosis with severe vacuolation and injury up to one-half; fat moderate. Recovery on mixed diet.

EXPERIMENT 21.—Dog 20-17, young black mongrel, female.

October 21: Weight, 20 pounds. In good condition and active; isolated after daily feeding; fasting begun.

October 22, 23 and 24: No food.

October 25: Weight, 18 pounds (8.18 kilos). Active. Gave subcutaneously 1.22 c.c. chloroform (0.15 c.c. per kilo) plus twice its volume liquid petrolatum, followed immediately by 1 gm. iodoxy-benzoic acid dissolved in 7 c.c. tenth-normal sodium hydroxid plus 10 c.c. of a 10 per cent. acacia solution subcutaneously. Temporary ether anesthesia.

October 26: Bright and active.

October 27: Active. Piece of liver removed at 1 p. m. Hard swelling in left lumbar quadrant at point of injection of iodoxy-benzoate. Sections show from 10 to 15 per cent. necrosis; very slight amount of fat over central half of lobules. Recovery on mixed diet. Slough at point of injection.

As will be noted from Table 2, massive doses of the organic oxidizing agents given subcutaneously apparently have protective value against chloroform injury; in some cases this is quite striking. Iodoxy-benzoic

TABLE 2.—Comparative Table—Subcutaneous Injections

Chloroform Alone						Chloroform and Oxidizing Agent						
Experiment Number	Dog Number	Fasting Period, Days	Chloroform C.c. per Kilo (subcutaneously)	Liver Injury	Remarks	Experiment Number	Dog Number	Fasting Period, Days	Chloroform C.c. per Kilo (subcutaneously)	Organic Oxidizing Agent (subcutaneously)	Liver Injury	Remarks
7	20-7	4	1.00	75% necrosis	Found dead on second day	19	20-38	4	0.20	Iodoxybenzoic acid 0.6 gm.	50-60% necrosis	Found dead on seventh day; apparently from toxemia, injection slough; liver repairing well
8	20-10	4	0.50	80% necrosis	Died on second day							
9	20-12	4	0.20	80% necrosis	Found dead on third day							
10	20-13	3	0.10	No necrosis; trace of fat	Minimal injury	20	20-65	4	0.22	Iodozobenzoic acid 0.5 gm.	60% (+) necrosis	Operation on second day; found dead on fourth day; debris in liver largely removed; dog developed distemper during experiment
11	20-13	3	0.20	75% necrosis	Found dead on third day							
12	20-18	4	0.16	70% necrosis	Found dead on next day	21	20-17	4	0.15	Iodoxybenzoic acid 1 gm.	10-15% necrosis; slightest possible trace fat	Recovered
13	20-17	4	0.15	35% necrosis; severe injury to ½	Recovered; see experiment 21 on same dog							
14	20-75	3	0.15	50% (+) necrosis	Operation on second day; found dead on fourth day	22	20-57	3	0.21	Iodozobenzoic acid 0.8 gm.	No necrosis; no fat	Liver sections from operation show glycogen; died on seventeenth day from pneumonia; injection slough
15	20-76	3	0.21	60% necrosis	Recovered; see experiment 23 on same dog; second control on same dog shows only about 50% necrosis	23	20-76	3	0.21	Iodozobenzoic acid 0.8 gm.	45% necrosis; very severely injured up to ½	Recovered; very slight injury from injection
16	20-31	4	0.18	55% necrosis	Found dead on second day; see experiment 24 on same dog	24	20-31	4	0.18	Iodoxybenzoic acid 0.5 gm.	Slightest possible trace necrosis; trace fat over ⅔	Recovered; injection slough
17	20-30	4	0.14	60% necrosis	Recovered; same result obtained on two occasions, once before and once after experiment 25							
18	20-106	4	0.14	85% necrosis	Died on second day	25	20-30	4	0.14	Iodoxybenzoic acid 0.5 gm.	45% necrosis	Recovered; injection slough

acid was dissolved in tenth normal sodium hydroxid about 0.1 gm. to 1 c.c., and the volume increased by addition of 10 per cent. acacia solution; no doubt the ugly sloughs obtained in such instances were due to the alkalinity of the solution (unfortunately much stronger than necessary), not to the drugs used; controls where alkaline solutions alone were used showed the same sloughs. Iodozo-benzoic acid was given suspended in 10 per cent. acacia solution; these injections did not cause such severe reactions, but the drug seemed to be absorbed only partially. With the exception of the sloughs already mentioned there have been no ill effects noted from injections of either drugs. On one occasion a large dose of iodozo-benzoic acid suspension was given to a dog intraperitoneally; this caused an acute reaction and contributed largely to the dog's death within a few hours (chloroform was given also, subcutaneously). Intraperitoneal injections of from 10 to 20 mg. iodozo-benzoic acid in rats sometimes seem very toxic, in other cases apparently cause no reaction.

It is interesting to note the very small doses of chloroform which may prove fatal when given subcutaneously to dogs after a preliminary fast. Experiments 10 and 11 indicate the narrow zone of safety between a dose producing no injury and that causing death.

Experiment 22 indicates superficially a very marked protection, but since the liver showed glycogen at operation, it may be a food protection, either because of an inadequate starvation period, or because of feeding by mistake on fasting days.

Table 3 merely amplifies experiments recorded in Table 2 and adds Experiments 26 and 27 to complete the record of Dog 20-30. Experiment 26 will be taken up later in discussing the use of cyanids. Experiment 27 is merely a repetition of 17, to act as double control. This double check was attempted on Dog 20-76 (Table 2), but the second trial with chloroform alone showed only about 50 per cent. necrosis, compared with the original 60 per cent.; this is the only time that two controls on the same animal have failed to check, and this is not a very wide fluctuation considering that estimations are merely relative.

It will be noted that Experiment 17 was intended as a control not only for Experiment 25 on the same animal, but for Experiment 16 on Dog 20-31; while Experiment 24 controls Experiment 16 on the same animal. A point worth noting is that the weights of these dogs in control experiments were less than in the others; in such cases the animals actually received less chloroform; but in the cases with greater weights the surplus fat may have been more than sufficient as a block to chloroform to compensate for the greater injection, ignoring any possible effect from organic oxidizing agents. However, no such

TABLE 3.—Effect of Iodoxy-Benzoate

	Experiment Number	Date of Injection	Fasting Period, Days	Weight at Time of Injection, Kilos	Chloroform, C.c. per Kilo (subcutaneously)	Potassium Cyanid (subcutaneously), Mg.	Iodoxybenzoic Acid (subcutaneously), Gm.	Amount of Liver Injury	Remarks
Dog 20-30 Small male terrier	17	11/10/19	4	5.80	0.14	..	...	60% necrosis; slightest possible trace fat	Questionable distemper during convalescence; wound healed slowly
	25	12/18/19	4	6.42	0.14	..	0.5	45% necrosis; slight trace fat	Iodoxy-benzoic acid dissolved in alkaline acacia solution; injection slough
	26	2/ 4/20	4	6.30	0.14	25	...	45-50% necrosis; slight trace fat	Potassium cyanid dissolved in 12 c.c. physiologic sodium chlorid solution
	27	3/22/20	4	6.02	0.14	..	...	60% necrosis; slight trace fat	Experiment performed as second control
Dog 20-31 Young female collie	16	11/10/19	4	6.00	0 18	..	0.5	Slightest possible necrosis; trace of fat over ⅔ of each lobule	Iodoxy-benzoic acid dissolved in alkaline acacia solution; questionable distemper during convalescence; injection slough
	24	12/18/19	4	5.68	0.18	..	...	55% necrosis; slightest possible trace fat	Alkaline acacia solution injected; found dead on second day; necrosis at point of injection; edema and congestion in lungs

explanation will hold in the case of Dog 20-76, for here the weights in control experiments were practically the same, and both slightly greater than the weights in experiments when other substances were injected, in which latter cases the injuries sustained were less.

The tables and protocols which follow present a few experiments in which cyanid were used in conjunction with chloroform.

EXPERIMENT 28.—*Control; Chloroform Anesthesia.* Dog 19-74, young black and white male terrier.

Dec. 7, 1918: Weight, 11.8 pounds. In good condition; fourth day of fasting; chloroform anesthesia for one and a quarter hours.

December 9: Weight, 11.1 pounds. Active. Piece of liver removed in afternoon; bled freely. Sections show necrosis involving one-half of each liver lobule, and a moderate degree of fatty degeneration in zone surrounding necrosis.

Chloroform Anesthesia; Cyanid Subcutaneously. Dog 19-74, a black and white male terrier.

Oct. 18, 1919: Weight, 15 pounds. In good condition; isolated before daily feeding; fasting begun. Since the control experiment (given above) was performed, this animal has been subjected to two experiments in which organic oxidizing agents were injected intravenously (Table 1), also a second control with result the same as in the first.

October 19 and 20: No food.

October 21: Weight, 13.9 pounds. Active. Chloroform anesthesia for one and a quarter hours. Gave 15 mg. potassium cyanid in 30 c.c. physiologic sodium chlorid solution subcutaneously in divided doses at intervals during anesthesia.

October 23: Weight, 13.3 pounds. Active. Piece of liver removed at 1:30 p. m.; many adhesions; considerable bleeding; some subcutaneous edema in area of injections (due to alkalinity of potassium cyanid). Sections show approximately 60 per cent. necrosis.

EXPERIMENT 15.—*Control; Chloroform Subcutaneously.* Dog 20-76, a young, black mongrel, female.

Jan. 24, 1920: Weight, 14.2 pounds. Active and in good condition. Isolated before daily feeding; fasting begun.

January 25: No food.

January 26: (Third day of fasting.) Weight, 12.9 pounds (5.85 kilos). At 5 p. m. gave 1.23 c.c. chloroform (0.21 c.c. per kilo) plus 2.5 c.c. liquid petrolatum subcutaneously; temporary ether anesthesia.

January 27: Weight, 12.4 pounds. Quite active.

January 28: Weight, 12.3 pounds. Dog in fair condition. Piece of liver removed at 3:30 p. m. Sections show 60 per cent. necrosis; fat plus.

EXPERIMENT 30.—*Chloroform Subcutaneously; Cyanid Subcutaneously.* Dog 20-76, a young, black mongrel female.

March 19: Weight, 14.8 pounds. In excellent condition. Isolated after daily feeding; fasting begun.

March 22: (Third day of fasting.) Weight, 12.9 pounds (5.85 kilos). Gave 1.23 c.c. chloroform (0.21 c.c. per kilo) plus 2.5 c.c. liquid petrolatum subcutaneously; followed immediately by 35 mg. potassium cyanid in 35 c.c. physiologic sodium chlorid solution subcutaneously; temporary ether anesthesia.

March 23: Active. Full diet.

March 24: Active. Piece of liver removed at 3:15 p. m. Sections show from 35 to 40 per cent. necrosis. Point of injection of potassium cyanid later showed a little local necrosis (due to alkalinity of potassium cyanid).

TABLE 4.—Potassium Cyanid as Influencing Chloroform Liver Injury

Experiment Number	Dog Number	Weight, Kilos	Fasting Period, Days	Chloroform	Potassium Cyanid (subcutaneously), Mg.	Liver Injury	Control Liver Injury (Same Dog)	Organic Oxidizing Agent Injection (Same Dog)	Remarks
28	19-74	6.3	4	1¼ hours anesthesia	15	60% necrosis	50% necrosis (chloroform anesthesia, no drugs—2 controls with same result)	50% necrosis (chloroform anesthesia; 0.14 gm. iodoxy-benzoic acid intravenously) 25% necrosis (chloroform anesthesia; 0.25 gm. iodozo-benzoic acid intravenously with question of feeding during starvation period)	Greater injury caused by potassium cyanid
29	20-17	8.6	4	0.15 c.c. per kilo subcutaneously	20	35-40% necrosis	35% necrosis (very severe injury up to ½)	10-15% necrosis (1 gm. iodoxy-benzoic acid subcutaneously)	A shade more necrosis in potassium cyanid experiment, but not so much surrounding injury
26	20-30	6.3	4	0.14 c.c. per kilo subcutaneously	25	45-50% necrosis	60% necrosis (2 controls with same result)	45% necrosis (0.5 gm. iodoxy-benzoic acid subcutaneously)	Less necrosis in potassium cyanid experiment than in controls; about the same as with organic oxidizing agent injection
30	20-76	5.9	3	0.21 c.c. per kilo subcutaneously	35	35-40% necrosis	(1) 60% necrosis (2) 50% necrosis	45% necrosis (0.8 gm. iodozo-benzoic acid subcutaneously)	Less necrosis in potassium cyanid experiment than in control or when using iodozo-benzoic acid

Between Experiments 15 and 30 came Experiment 23 in which the dog was given iodozo-benzoic acid subcutaneously (Table 2). In May this dog was used for another control similar to Experiment 15, and showed approximately 50 per cent. necrosis. In a final experiment in June the dog was given 26 mg. sodium cyanid (molecular equivalent of the 35 mg. potassium cyanid in Experiment 30), but 12 mg. of this were injected intraperitoneally and death occurred from respiratory failure in about one hour.

EXPERIMENT 35.—*Chloroform Anesthesia; Sodium Cyanid Intravenously.* Dog 21-18, a brindle mongrel, male; right eye shows keratitis and staphyloma, suggesting previous distemper infection.

Sept. 14, 1920: Weight, 25.5 pounds. In good condition and active. Isolated after daily feeding; fasting begun.

September 15, 16, 17. No food.

September 18: Weight, 23.8 pounds. Active. Chloroform anesthesia for forty-five minutes (3 to 3:45 p. m.). During thirty-five minutes of anesthesia 10 mg. sodium cyanid in 100 c.c. physiologic sodium chlorid solution were given intravenously (0.01 per cent. solution = approximately 1/500 N). Considerable chloroform was administered, but some respiratory difficulty was encountered because of sodium cyanid. More than the 100 c.c. would have been given except for shallow breathing, tendency to apnea, and a rapid, weak pulse.

September 19: Weight, 23.3 pounds. A little dull. Casein feeding.

September 20: Weight, 23.5 pounds. Somewhat dull. Casein feeding. Operation at 3 p. m. Piece of liver removed; liver is grossly injured. Sections show about 35 per cent. necrosis and a trace of fat.

EXPERIMENT 36.—*Chloroform Anesthesia; Physiologic Sodium Chlorid Solution Intravenously.* Dog 21-18. A brindle, mongrel male.

Oct. 19, 1920. Weight, 30.7 pounds. Bright and active. Wounds of former operations healed. Isolated after daily feeding; fasting begun.

October 20, 21 and 22: No food.

October 23: Weight, 27.5 pounds. Active and in good condition. Chloroform anesthesia for forty-five minutes (3:40 to 4:25 p. m.). Gave 100 c.c. physiologic sodium chlorid solution intravenously during anesthesia.

October 24: Weight, 27 pounds. Quite active. Gelatin feeding.

October 25: Weight, 25.5 pounds. Active. No vomiting. Operation at 2:30 p. m. Piece of liver removed; liver appears injured in gross. Sections show approximately 55 per cent. necrosis and a moderate amount of fat.

The experiments in which potassium cyanid was given subcutaneously appear very irregular and contradictory. On account of the immediate toxicity, the drug was given cautiously in rather small dosage; however, this accounts in no way for the fact that some cases show even less injury than the control experiments on the same animals; it may be coincidence that the larger doses of potassium cyanid (25 and 35 mg.) seem to have been somewhat protective. It will be recalled that we found no effect on chloroform liver injury from small intravenous injections of potassium cyanid.

Since in one case a small area of necrosis appeared at the point of injection of potassium cyanid, and in other cases moderate tissue edema

TABLE 5.—Sodium Cyanid Intravenously as Influencing Chloroform Liver Injury

Experiment Number	Dog Number	Weight, Pounds	Fasting Period, Days	Chloroform Anesthesia, Min.	Sodium Cyanid Intravenously, Mg.	Liver Injury	Remarks
31	20-108	17.5	4	45	..	60% necrosis	Control. Recovery; operation on second day following anesthesia
32	20-112	14.8	4	45	..	70% necrosis	Control. Found dead on second day following anesthesia
33	20-119	28.6	4	45	18	60% (+) necrosis; fat very extensive almost to lobule peripheries	Sodium cyanid in physiologic sodium chlorid solution, 1 mg. to 10 c.c.; intervals of accelerated breathing during anesthesia; periods of apnea the last few minutes; recovery; operation on second day following chloroform
34	20-119	27.4	4	45	..	75% (+) necrosis; fat moderate	Control (see Experiment 33). Found dead on second day following anesthesia
35	21-18	23.8	4	45	10	35% necrosis; trace of fat	Sodium cyanid in physiologic sodium chlorid solution, 1 mg. to 10 c.c.; tendency to apnea and rapid, weak pulse, especially toward the last; recovery; operation on second day
36	21-18	27.5	4	45	..	55% necrosis; fat moderate	Control (see Experiment 35). 100 c.c. physiologic sodium chlorid solution intravenously during anesthesia; recovery; operation on second day

was manifested, we must conclude that a considerable local reaction took place (due in part to alkalinity of the drug), and it seems likely that not only the tissue suffered but that a certain part of the potassium cyanid may have been destroyed locally.

Table 5 gives the results of sodium cyanid injections in two dogs; these same animals were later used as controls; two other control experiments on different animals are also included. These experiments indicate that the cyanid may have some protective value against chloroform injury. The attempt was made to give the anesthetic at the same rate in all cases, but on account of respiratory difficulties caused by the cyanid it is possible that the animals receiving such injections were given somewhat less chloroform. This is suggested as a possibility only, but if so might account for the lessened liver necrosis in such cases. For comparative purposes we consider that controls on the same animals are by far the most valuable.

DISCUSSION

Although these experiments were undertaken to throw some light on the rôle of oxidations in chloroform liver injury, the results are far from conclusive. There appears to have been a definite amount of protection in the cases when organic oxidizing agents were injected in large amounts subcutaneously. Should this have been because an increased supply of oxygen was furnished to a liver hampered by its lack, we should have expected cyanids to have acted in an opposite manner, as found by Loevenhart, Amberg and their associates in various conditions; as a matter of fact, relatively large doses of cyanids seem to have been themselves rather protective in certain instances.

Administration of cyanids intravenously during chloroform anesthesia has been difficult because of respiratory irregularities; this trouble has been much more marked than in control experiments (without the cyanid). Loevenhart has had less difficulty in giving a solution of sodium cyanid five times as concentrated as that used by us. There are two factors in our experiments which may account, in part, for this high immediate cyanid toxicity: (1) preceding fasting period, and (2) simultaneous chloroform anesthesia.

We are safe in saying that the experiments do not prove that liver necrosis following administration of chloroform has any connection with a disturbance of normal tissue oxidation.

At the present state of our knowledge it is hardly justifiable to assume that chloroform narcosis and chloroform liver necrosis are manifestations of the same pharmacologic property of the drug; this point is often left rather indefinite in the literature on the subject. It is relatively simple to obtain one without the other. Since our observa-

tions relate entirely to the phenomenon of liver injury, we do not extend our deductions to bear at all upon the existing theories pertaining to the anesthetic action of chloroform.

SUMMARY

Very small amounts of chloroform given subcutaneously are sufficient to cause an extensive liver injury in fasting animals.

The intravenous injection of small amounts of organic oxidizing agents (iodoxy- and iodozo-benzoic acids and their sodium salts) seems to have no effect on chloroform liver necrosis. Large amounts of these substances subcutaneously appear to afford the liver some protection against chloroform injury.

The administration of cyanids (potassium and sodium) does not effect chloroform liver injury in any constant manner; it seems that large doses may exert some protective action.

These experiments offer no evidence that chloroform liver injury is a result of disturbance in tissue oxidations.

ON THE ETIOLOGY OF AN OUTBREAK OF INFECTIOUS DIARRHEA *

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In the late summer and autumn of 1918, an outbreak of infectious diarrhea occurred at the St. Anne Barracks, Nantes, in Base Section No. 1, A. E. F. In the course of an investigation of this outbreak, I isolated a micrococcus from a number of cases which shows evidence of being the etiologic agent.

Infectious diarrhea had been prevalent throughout the base section, especially in the camps in the vicinity of St. Nazaire, and epidemics of a similar nature had been reported in other parts of France. The prevalence of infectious diarrhea throughout the A. E. F. was known to practically all the members of it, and particularly to those who were directly concerned with the control of the communicable diseases. There are no data available giving the exact number of cases that occurred. Repeated attempts to obtain information resulted only in approximations based on the total strength of the command. These estimates varied from an incidence of 25 to 100 per cent.

The outbreaks of infectious diarrhea were ascribed to a number of different probabilities, mainly dietary faults. Investigation shows, however, that the disease was infectious in character, spreading from organization to organization, that it was initiated during the summer months, reaching a climax during the late summer and early autumn and finally declining with the beginning of cold weather. A number of investigators believed the outbreaks to be infections with *B. dysenteriae*, despite the fact that there was no bacteriologic evidence to support such a view. The endemicity of bacillary dysentery in the A. E. F. may have influenced the formation of such opinion, but in no case of true infectious diarrhea were dysentery bacilli found in a sufficient number of cases to account for the outbreak. A contributory cause of this confusion was the failure to distinguish between infectious diarrhea and bacillary dysentery.

Infectious diarrhea is a mild nonfebrile disease of short duration characterized by symptoms of an irritating enteritis; and a distinction is drawn between that type of outbreak and bacillary dysentery.[1]

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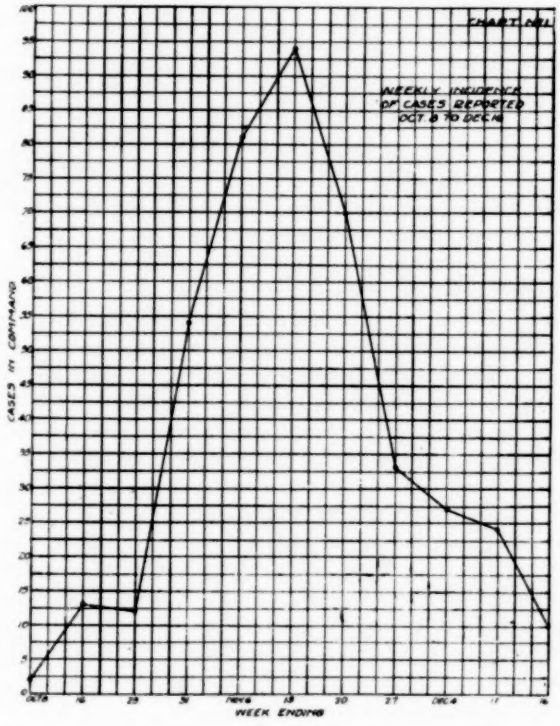
1. Though infectious diarrhea is a generic term which includes acute infections with *B. dysenteriae*, I would, for purposes of simplicity and convenience, limit the term to the milder diarrheas of unknown etiology and speak of the more severe type caused by the dysentery bacilli as dysentery. The terms are used in that sense in this paper.

The two diseases are clinically distinct. Infectious diarrhea is characterized by a mild diarrhea developing suddenly, and accompanied by cramps in the abdomen and occasionally by vomiting. The cramps are not continuous, but come on spasmodically. There are no marked, general symptoms, such as fever, except that there results a feeling of depression and weakness due to the frequent evacuations. The symptoms are local and purely intestinal. Recovery usually occurs in from three to five days after purgation. A small percentage of cases show more severe reactions, with slight fever, and require hospitaliza-



tion. These exceptionally severe cases are usually discharged recovered in about two weeks. The diarrhea is watery, voluminous and explosive, light to dark brown in color and does not contain blood or mucus. On the other hand, most cases of bacillary dysentery progress rapidly to a much more severe condition, and almost all require hospitalization. The cramps, unlike those in infectious diarrhea, are more continuous and much more severe. There is tenesmus and irritation of the anus. The stools are mucoid to mucosanguineous in character. There is

usually a marked general reaction with fever ranging from 100 to 105 F., and evidences of toxemia. Finally, bacillary dysentery is associated with *B. dysenteriae* which is not found in infectious diarrhea.

Infectious diarrhea is prevalent among the French population during the summer months, and constitutes the largest part of the summer diarrhea of infants. The difference between it and true dysentery is recognized by French physicians, and various local names are used to distinguish it. In St. Nazaire and its vicinity, the disease is known as "la Croisicette" or "la Sablaise," the names being derived from two towns, la Croisic and les Sables d'Olonne, respectively, south and north of St. Nazaire, where it is believed the outbreaks find their endemic focus each summer, and spread to the surrounding country.

Most of the early workers on infectious diarrhea devoted themselves to the identification of organisms in the stools of diarrhea patients. A number attempted to prove an etiologic relationship. Cumston,[2] in one of the earliest papers on the subject, expressed his belief that *B. coli* can become virulent and so cause infantile diarrhea. Escherich [3] isolated a streptococcus that was pathogenic for white mice. Booker,[4] Baginsky,[5] Tomkins,[6] Czerny and Moser,[7] Lesage,[8] Hirsh,[9] Delepine [10] and others, described a variety of organisms representing the bacterial flora in diarrhea cases, but in no case were these investigators able to prove a causal relationship to the disease. Morgan [11] isolated a number of organisms, among them some gram-negative bacilli intermediate between the paratyphoid and dysentery organisms which were pathogenic for rats.

Booker [12] concludes that "no single micro-organism is found to be the specific exciter of the summer diarrhea of infants . . ." It is interesting, however, to note his observation in an investigation of ninety-two cases, that "Micrococci are present in all of the cases, in immense numbers in some, being fewer in others. In some cases they fail to grow on culture mediums, but appeared in great numbers in cover-slip preparations from the intestinal contents and in hardened sections of the intestines."

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2. Cumston: Internat. M. Mag., February, 1897.
3. Escherich: Wien. klin. Wchnschr. 1897, No. 42.
4. Booker: Ninth Internat. Med. Cong., III, p. 598, 1887.
5. Baginsky: Berl. klin. Wchnschr., 1889, Nos. 46, 47 and 49; Arch. f. Kinderh. **12**: Pt. 2, 1890.
6. Tomkins: Brit. M. J. **2**:180, 1889.
7. Czerny and Moser: Jahrb. f. Kinderh. **38**:4, 1894.
8. Lesage: Semaine méd., Oct. 16, 1897.
9. Hirsh: Centralbl. f. Bakteriol. **22**: Nos. 14 and 15.
10. Delepine, S.: J. Hygiene **3**:68, 1903.
11. Morgan: Brit. M. J. **1**:908, 1906.
12. Booker: Johns Hopkins Hosp. Rep. **6**: 1897.

Following the identification of the various dysentery bacilli [13] a number of investigators atempted to determine the relation of these organisms to infant diarrhea. In a series of investigations published in 1904 by Bassett,[14] Gay and Stanton [15] and Duval and Bassett [16] on 417 cases of summer diarrhea, 67 per cent. yielded the dysentery bacillus. With very few exceptions they were of the "Harris" type. In the large majority of the cases either blood or mucus was present in the stools, and it is evident that these workers were dealing with dysentery outbreaks. It is interesting, however, that in the cases in which neither blood nor mucous was present, no dysentery bacilli were isolated. Rotch [17] concludes, after an examination of sixty-one cases, only 16 per cent. of which showed the presence of dysentery bacilli, that "the infectious diarrheas are probably caused by a variety of organisms. The *B. dysenteriae* has been proved to be one cause, though not yet the sole cause." Collins [18] in "a study of the dejecta of normal children and those suffering from acute and subacute diarrhea, with special reference to *B. dysenteriae*," failed to find the organism present and concluded that it "would lead us to suspect some cause or combination of causes other than this organism as the etiological factor in these conditions."

Other attempts to determine the presence of dysentery bacilli in cases of infant diarrhea were made by Duval and Bassett [19] who found forty-two out of fifty-three cases positive, Wollstein [20] who found 39 out of 114 cases positive, Michael [21] who found twenty-four out of ninety-seven cases positive, Dunn [22] who found only ten out of sixty-one cases positive, and Schwartz [23] who failed to find the organism in thirty cases that he investigated. Weaver and Tunnicliff [24] found that only 25.4 per cent. yielded organisms culturally similar to *B.*

13. Shiga: Centralbl. f. Bakteriol. **23**:1898; **24**: 1898; Deutsch. med. Wchnschr. **43**: **44**: **45**: 1901. Flexner: Phila. M. J. **6**: 1900; Bull. Johns Hopkins Hosp. **11**: 1900. Strong and Musgrave: Rep. Surg.-Gen. U. S. Army, Washington, 1900. Kruse: Deutsch. med. Wchnschr. **26**: 1900; **27**: 1901. Hiss and Russell: Med. News, February, 1903.

14. Bassett: Studies Rockefeller Inst. **2**:88, 1904; Lewis: ibid. **2**:82, 1904; Kendall: ibid. **2**:76, 1904; Waite: ibid. **2**:72, 1904; Duval: ibid. **2**:42, 1904; Wollstein: ibid. **2**:55, 1904; Cordes: ibid. **2**:67, 1904.

15. Gay and Stanton: Studies Rockefeller Inst. **2**:61, 1904.

16. Duval and Bassett: Studies Rockefeller Inst. **2**:7, 1904.

17. Rotch: Am. Med. **2**:737, 1904.

18. Collins: J. Infect. Dis. **2**: (Nov. 25) 1905.

19. Duval and Bassett: Am. Med. **4**:417 (Sept. 13) 1902.

20. Wollstein: J. M. Research **10**:11, 1903.

21. Michael: J. Infect. Dis. **2**: (Jan. 12) 1905.

22. Dunn: Am. Med. **7**:737, 1904.

23. Schwartz: Proc. New York Path. Soc. **3**:172, 1903.

24. Weaver and Tunnicliff: J. Infect. Dis. **2**: (Jan. 12) 1905.

dysenteriae out of a series of 102 cases. They conclude that "we are unacquainted with a specific cause for all cases of summer diarrhea in infants."

English workers [25] appear to have been more precise in distinguishing between epidemic diarrhea and bacillary dysentery, and concerned themselves more particularly with the question of the source of these outbreaks and the transmissability of the disease. The general concensus of opinion of these English investigators points to the "fly carrier" as the most probable line of communication.

Taylor and Knapp, in a report to the base surgeon, Base Section No. 1, on the gastro-intestinal disorders occurring in the vicinity of St. Nazaire indicate the presence of two distinct types. They regard all cases which show blood and mucus as probably being due to *B. dysenteriae*, and are of the opinion that the milder type is of an infectious nature, the etiology being unknown.

FIELD INVESTIGATION

In a field investigation made Dec. 15 and 16, 1918, I found that a considerable number of cases of diarrhea had occurred in and around the camp at St. Anne on the outskirts of Nantes. A number of these

TABLE 1.—NUMBER OF CASES OF DIARRHEA REPORTED, ST. ANNE BARRACKS, NANTES (SEPTEMBER)

Organization	September, 1918										
	4	5	6	7	8	9	10	11	12	14	16
824th Co. 826th Labor Btn.	...	3	...	...	1	1	1	...	...	2	1
Co. A. 306th Labor Btn.	1	...	...	...	...	...	1	...	1	...	...
Det., Co. C, 513th Engrs.	1	...	2	1	1	...	...	1	...	1	...
Total	2	3	2	1	2	1	2	1	1	3	1

had occurred before and during the month of August of which there were no available records. The "sick books" showed that nineteen cases occurred during the early part of September, three organizations being involved. These were the first recorded cases and were reported as shown in Table 1.

The occurrence of these cases indicated at that time nothing of epidemiologic significance. They probably formed the initial outbreak from which the subsequent epidemic took its focus. No record was kept of any cases that may have occurred during the latter part of September. Two new cases occurred during the first week of October, and from then on there was a steady increase until the week ending

25. Notter: Proc. Roy. Soc. Med., Lond., Epid. Sect., Pt. 2, p. 263, 1910; Niven: ibid. **3**: Pt. 2 (April 7) 1910; Sandilands: ibid. Feb. 25, 1910; Parsons; ibid., Pt. 2, p. 269 (June) 1910; Peters: J. Hygiene **10**:1910; Newsholme: Practitioner, August, 1912.

November 14 when ninety-four new cases were reported. A gradual decline followed. During the week ending December 11, twenty-four new cases occurred and from December 12 to 16, ten cases were reported. The cases and their corresponding organizations are given in Table 2. A graphic representation of this outbreak is given in the accompanying chart.

The primary sporadic outbreak and the subsequent epidemic following about two weeks later indicated some infectious agent which gradually spread through the various organizations, as shown in Table 2. During the first week one organization only was affected, during the second week it spread to three more and during the third, fourth and fifth weeks to two, three and two more respectively until ultimately the whole command with the exception of a Chinese battalion of 182 men had developed cases.

TABLE 2.—CASES OF DIARRHEA REPORTED BETWEEN OCTOBER 1 AND DECEMBER 16*

Organization	Total Strength	Week Ending										Dec. 12 to Dec. 16
		October				November				December		
		8	16	23	31	6	13	20	27	4	11	
806th Co., 824th Lab. Btn.	226	2	7	6	13	23	25	22	6	4	3	0
Co. D, 308th Lab. Btn.	246	0	2	1	6	10	12	5	5	1	6	0
Co. A, 306th Lab. Btn.	138	0	3	1	17	22	9	2	4	4	3	2
Casual Co., No. 1	26	0	1	2	7	7	8	6	3	4	2	6
Co. C, 513th Engrs.	57	0	0	1	2	2	5	6	2	0	7	0
Co. B, 516th Engrs.	40	0	0	1	1†							
Co. B, 315th Lab. Btn.	45	0	0	0	3	5	3	3	1	1	0	0
Q. M. C. Detachment	150	0	0	0	1	2	2	7‡				
336th M. G. Bat. Cos. C & D	320	...	...	...	4§							
Co. C, 701st Stev. Btn.	169	0	0	0	0	11	11	8	4	1	0	0
Co. A, 315th Lab. Btn.	127	0	0	0	0	1	19	11	8	12	3	2
Totals	1,544	2	13	12	54	83	94	70	33	27	24	10

* Total cases, 422; morbidity rate, 27.3 per cent.
† Left camp after week of October 31.
‡ Left camp after week of November 20.
§ In camp only two weeks.

A sanitary survey was made, the barracks, latrines and kitchens being examined. Particular attention was given to the mess, especially as regards the difference between the food served and methods used by the affected organizations and the nonaffected Chinese battalion; the assumption being that there might be more than a difference in racial resistance to explain it. It was found that practically nothing was served in the Chinese mess which had not previously been boiled. The ration consisted of a regular diet of meat soup, rice and tea. Raw water was never used, tea being substituted. The water was the same as that supplied to the city of Nantes in which no considerable outbreak of diarrhea had been observed.

In all the kitchens a large number of flies were found for the season of the year, and inquiry determined that they had been a considerable pest until about four weeks previous to the investigation. This evidence and the fact that the initial outbreak occurred during the height of the fly season and that the epidemic began to wane immediately after the fly season ended, and kept continually dropping off as they disappeared, and the particular manner in which the disease spread from organization to organization lends countenance to the possibility that they were a channel of infection. Though the closets in which bread and meat were kept were sufficiently well screened, no attempt was made to screen the kitchens themselves and exposed food was in that manner unprotected.

LABORATORY INVESTIGATION

Specimens of blood, urine and feces were obtained from eight cases. The course of the disease was relatively mild, only fifteen patients out of a total of 422 requiring hospitalization. Of these, six had been discharged prior to this investigation. One had developed pneumonia and was unavailable for experimental study.

TABLE 3.—CASES AND ISOLATIONS

Case	Name	Ward	Source of Isolations		
			Feces	Urine	Blood
1	Williams	A10	Negative	15, 16, 17	Negative
2	Clark	A 9	Negative	20, 21	Negative
3	Gathright	A 9	25, 26	27, 28	29
4	Hodgkins	A 9	Negative	Negative	Negative
5	Bowden	414	3, 4	11, 12, 13	Negative
6	Ashford	416	1, 2	9, 10	Negative
7	Langford	A10	5, 6, 7, 8	Negative	Negative
8	Williams	414	Negative	18, 19	Negative

The numbers designate strains.

Isolation of the Organisms.—The specimens were plated on a carefully balanced neutral Endo medium containing the minimum amount of fuchsin and sodium bisulphite commensurate with a good color reaction. A gram-positive micrococcus was isolated in four cases from the feces, in six cases from the urine and in one case from the blood. Seven cases yielded this coccus from one or more sources, in several instances in almost pure culture. One convalescent case was negative (Table 3). The colonies appear as small colorless droplets after overnight incubation, that later grow pink, due to slow fermentation of the lactose.

Morphology and Growth.—The organism is a small gram-positive micrococcus varying considerably in the size of the individuals and in the degree of retention of the gram stain. The larger forms show a tendency to take the counter strain. They are irregularly round and

flattened at the adjacent surfaces, occurring in diploforms or in aggregates of diploforms. The colonies are small, colorless, to slightly bluish and transparent becoming later grayish and umbilicated and present a "dry surface" appearance as they get older. The coccus develops readily on neutral infusion agar, but never produces more than a delicate confluent growth.

TABLE 4.—Fermentation Reactions

Fermentation Mediums Containing	Strains							
	No. 19	No. 11	No. 16	No. 26	No. 15	No. 30	No. 28	No. 4
Dextrose	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid
Mannite	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid
Maltose	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid
Lactose	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid
Sucrose	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid
Xylose	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.
Rhamnose	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Inosite	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Arabinose	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.
Inulin	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Dextrin	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.	Rdn.
Raffinose	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Salicin	Acid	Acid	Acid	Acid	Acid	Acid	Acid	Acid

Rdn. = reduction.

Fermentation Reactions.—The strains were tested on dextrose, mannite, maltose, lactose and sucrose broth. They fermented all with acid, but no gas formation. No other fermentable substances were available at that time, but subsequent tests carried out on a larger variety of mediums with eight strains successfully transported to the United States showed that the strains were identical in their biological activity. The results are given in Table 4.

TABLE 5.—Agglutination of Patient's Serum with Homologous Strains. Case 1

Source of Strain	Strain No.	Serum Dilutions					Human Serum Control 1:10	Salt Solution Control
		1:10	1:20	1:40	1:80	1:160		
Urine	15	++	++	++	+	+	—	—
		++	++	++	++	++	—	—
Urine	17	++	++	++	++	++	—	—
		++	++	++	++	++	—	—

± indicates slight agglutination, + indicates agglutination without sedimentation, and ++ indicates agglutination with sedimentaton.
Upper readings taken after 8 hours incubation.
Lower readings taken after 18 hours incubation.

Agglutination reactions: Serums obtained from four cases during the period from the tenth to the fourteenth day of the disease were tested against the organisms isolated from these cases. The agglutinations were carried out at 37.5 C. (water bath) and readings were taken after eight and eighteen hours. The results are given in Tables 5 to 8 inclusive.

TABLE 6.—AGGLUTINATION OF PATIENT'S SERUM WITH HOMOLOGOUS STRAINS. CASE 2

Source of Strain	Strain No.	Serum Dilutions 1:10	1:20	1:40	1:80	1:160	Human Serum Control 1:10	Salt Solution Control
Urine	20	+	++	++	++	+	—	—
		++	++	++	++	++	—	—
Urine	21	±	+	+	++	+	—	—
		++	++	++	++	++	—	—

Upper readings taken after 8 hours incubation.
Lower readings taken after 18 hours incubation.

TABLE 7.—AGGLUTINATION OF PATIENT'S SERUM WITH HOMOLOGOUS STRAINS. CASE 5

Source of Strain	Strain No.	Serum Dilutions 1:10	1:20	1:40	1:80	1:160	Human Serum Control 1:10	Salt Solution Control
Feces	3	±	+	+	++	+	—	—
		++	++	++	++	++	—	—
Feces	4	++	++	++	++	+	—	—
		++	++	++	++	+	—	—
Urine	11	±	+	++	++	++	—	—
		++	++	++	++	++	—	—
Urine	12	±	+	+	++	+	—	—
							—	—
Urine	13	±	+	+	±	±	—	—
		±	++	++	+	+	±	±

Upper readings taken after 8 hours incubation.
Lower readings taken after 18 hours incubation.

TABLE 8.—AGGLUTINATION OF PATIENT'S SERUM WITH HOMOLOGOUS STRAINS. CASE 6

Source of Strain	Strain No.	Serum Dilutions 1:10	1:20	1:40	1:80	1:160	Human Serum Control 1:10	Salt Solution Control
Feces	1	—	±	±	±	+	+	—
		+	+	+	+	+	±	±
Feces	2	±	±	±	±	±	—	—
		+	+	±	±	±	—	—
Urine	9	±	±	±	±	±	—	—
		+	++	+	+	+	—	—
Urine	10	±	±	±	±	±	—	—
		±	±	±	+	+	—	—

Upper readings taken after 8 hours incubation.
Lower readings taken after 18 hours incubation.

It is evident from the series of agglutination reactions given in Tables 5 to 8 that the serum of persons recovering from the disease

contains specific agglutinins against the strains isolated from the same cases.

Cross agglutinations were next carried out, using the two most potent human serums (Cases 1 and 2) against all the heterologous strains isolated from other cases. The results are given in Tables 9 and 10.

TABLE 9.—Cross Agglutinations. Serum from Case 1

Strain No.	Source	Serum Dilutions				Salt Solution Control
		1:20	1:40	1:80	1:160	
1	Feces	+	+	+	+	±
2	Feces	−	±	±	±	−
9	Urine	++	±	−	−	−
10	Urine	+	±	−	−	−
3	Feces	±	±	±	−	−
4	Feces	+	+	+	+	−
11	Urine	+	+	+	−	−
12	Urine	+	+	+	−	−
13	Urine	+	+	+	+	+
5	Feces	+	+	±	±	−
6	Feces	++	±	−	−	−
7	Feces	++	+	−	−	−
8	Feces	++	+	−	−	−
18	Urine	+	+	+	+	−
19	Urine	−	±	+	±	−
20	Urine	−	±	+	±	−
21	Urine	−	+	+	−	−
25	Feces	+	+	+	+	−
26	Feces	−	+	±	−	−
27	Urine	−	+	+	+	−
28	Urine	−	−	−	−	−
30	Blood	−	−	−	−	−

TABLE 10.—Cross Agglutinations. Serum from Case 2

Strain No.	Source	Serum Dilutions			Salt Solution Control
		1:40	1:80	1:160	
1	Feces	++	+	+	±
2	Feces	++	++	++	−
9	Urine	++	++	++	−
10	Urine	++	++	++	−
3	Feces	++	++	++	−
4	Feces	++	++	++	−
11	Urine	+	+	++	−
12	Urine	++	++	++	−
13	Urine	+	+	+	±
5	Feces	++	++	++	−
6	Feces	++	+	+	−
7	Feces	++	+	+	−
8	Feces	++	+	−	−
15	Urine	−	−	−	−
16	Urine	−	+	+	−
17	Urine	+	−	−	−
18	Urine	+	+	+	−
19	Urine	±	±	±	−
25	Feces	++	++	++	−
26	Feces	++	+	−	−
27	Urine	±	+	−	−
28	Urine	−	−	−	−
30	Blood	−	−	−	−

Of the twenty-five strains tested against the two heterologous serums, all but three (Strains 15, 28 and 30) were agglutinated. These three strains were among the eight surviving strains transported to this country and were subsequently tested after a series of transplants

against a highly potent rabbit serum. All three were agglutinated (Table 11).

Animal Experiments: Attempts to reproduce the disease in rabbits failed. Young and old rabbits were fed with mixed cultures; the results were uniformly negative.

Macacus rhesus monkeys were next used with the following results:

MONKEY No. 1.—A *Macacus rhesus* monkey was fed 10 c.c. of mixed broth cultures of eight strains on three successive days. Twelve days after the last feeding the animal showed signs of illness with very profuse diarrhea on the thirteenth day. He died on the fourteenth day.

Feces collected on the thirteenth day were plated. A great many characteristic colonies developed which showed the typical micrococcus in smear preparation. Six fishings proved to be identical by fermentation and agglutination reactions with the organism previously described.

At necropsy, the lungs, heart, spleen, kidneys and gallbladder were found normal. The mesentery was considerably injected, and showed a hyperemia indicating an acute condition. The mesenteric lymph nodes were found con-

TABLE 11.—AGGLUTINATION REACTIONS, RABBIT SERUM (STRAIN 5, CASE 7)

Case	Strain No.	Dilutions			Salt Solution Control
		1:100	1:1,000	1:10,000	
1	15	++	±	—	—
1	16	++	±	±	—
3	26	++	+	—	—
3	28	++	—	—	—
3	30	++	—	—	—
5	4	++	++	++	—
5	11	++	+	—	—
8	19	++	—	—	—

siderably reddened. There was slight hyperemia of the small intestine. The organism was present in direct smear preparation and section in the mesenteric lymph nodes and spleen. It was isolated in pure culture from mesenteric lymph nodes and heart's blood.

MONKEY No. 2.—A second monkey was subsequently fed with the living bacteria filtered free from the broth in which they had been grown and incorporated as part of a banana paste. The animal was fed on three successive days with the bacteria filtered from 10 c.c. of culture. On the fifth day he developed a diarrhea but rapidly recovered.

MONKEY No. 3.—A third monkey was fed on three successive days with 10 c.c. of mixed broth cultures by means of a stomach tube. He died eight days after the first feeding. At necropsy a pathologic condition was found at the juncture of the large and small intestine which resembled an acute colitis and a small patch was found in the wall of the small intestine. There was marked injection along the colon. Micrococci were found in the mesenteric lymph nodes and spleen.

MONKEY No. 4.—One monkey was fed on three successive days with 10 c.c. quantities of the sterile filtrate from twenty-four hour broth cultures. The feeding was carried out by means of a stomach tube. The animal remained normal and showed no symptoms.

MONKEY No. 5.—This animal was similarly fed, but bacteria killed by heating at 60 C. for twenty minutes were used. The monkey remained normal and showed no symptoms.

MONKEY No. 6.—This monkey was actively immunized with a polyvalent bacterial vaccine made from the eight cultures and killed at 60 C. for twenty minutes. Three doses of 1 c.c. each were given subcutaneously at intervals of one week. Two weeks later the animal was fed 10 c.c. of mixed cultures of the living bacteria on three successive days by means of a stomach tube. No symptoms developed.

MONKEY No. 7.—It was attempted to passively immunize this monkey by means of rabbit sera produced against the eight strains. Four c.c. of the pooled rabbit serum was given intraperitoneally. The animal was fed with 10 c.c. of the mixed broth cultures by means of a stomach tube on three successive days. Death occurred fifteen days after the first feeding. The necropsy showed the lung, liver and kidneys to be normal. There was definite injection along the colon and the omentum was hemorrhagic. The mesenteric lymph nodes were slightly reddened. Micrococci were present in the spleen and mesenteric lymph nodes by direct smear and in section. The organisms were isolated from both sources and were proved identical by agglutination.

SUMMARY AND CONCLUSIONS

1. Infectious diarrhea, as defined, and dysentery are two distinct diseases, differentiated clinically and bacteriologically. The main clinical differences are that infectious diarrhea is a mild disease of short duration with local manifestations and no general symptoms. The symptoms are chiefly intestinal. Blood or mucous is not present in the stools. Bacillary dysentery is usually very much more severe and of longer duration; there is a marked general reaction with fever and evidence of toxemia. The stools usually contain blood or mucous. For our present purpose we have defined dysentery as that disease caused by *B. dysenteriae*, and infectious diarrhea as that variety of outbreaks which are more mild and are at present of unknown etiology.

2. Infectious diarrhea is probably transmitted in much the same manner that other enteric diseases are spread, one of the agencies being flies.

3. Of eight cases in which urine, feces and blood were examined, seven yielded a gram-positive micrococcus from one or more sources, which were biologically identical in their reactions on fermentation mediums. The organisms were agglutinated by the serum of patients from which they were obtained, and also by the serum of other patients. Three strains that did not agglutinate when first isolated were subsequently agglutinated by rabbit serum produced with a heterologous strain.

4. Rabbits are resistant to infection by this organism. Old and young rabbits were used, but the results were uniformly negative.

5. *Macacus rhesus* monkeys were fed with mixed strains. One monkey died on the fourteenth day after a profuse diarrhea on the thirteenth day from which the organism was isolated. It was subsequently isolated at necropsy from the mesenteric lymph nodes and the spleen. A second monkey fed with cultures, filtered free from the

broth in which they had been grown, developed a diarrhea on the fifth day and recovered. A third monkey was fed with mixed broth cultures by means of a stomach tube. He died on the eighth day. A pathologic condition was found at the juncture of the large and small intestine and the organism was found in the mesenteric lymph nodes and spleen.

Two monkeys, one fed with the sterile filtrate from broth cultures and the other with cultures killed by heating at 60 C. for twenty minutes developed no symptoms and remained alive.

One monkey actively immunized by a polyvalent vaccine made from these cultures was subsequently resistant to infection.

One monkey that we attempted to immunize passively by injection with specific rabbit serum died fifteen days after feeding, and the organism was isolated at necropsy from the spleen and mesenteric lymph nodes.

These experiments indicate that the organism is pathogenic for *Macacus rhesus* monkeys, produces no exotoxin or endotoxin and can be used to produce active immunity against subsequent infection.

6. The sum of evidence presented in this paper suggests the etiologic relationship of the organism described to infectious diarrhea in the outbreak studied.

I wish to acknowledge my indebtedness to Mr. Robert V. B. Emmons, Private, U. S. Medical Corps, who aided me materially in the early part of this work in France; to Prof. M. J. Rosenau whose interest and aid enabled me to carry it on to a conclusion in this country, and to Prof. J. Bronfenbrenner for his valuable constructive criticism. Miss Lila Spence has given me her technical assistance and I thank her for her kind and efficient help.

THE INTRAVENOUS USE OF FOREIGN PROTEIN IN THE TREATMENT OF CHRONIC CASES OF ARTHRITIS

WITH SPECIAL REFERENCE TO THE USE OF SECONDARY PROTEOSE.*

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In a paper already published by one of us,[1] the value of intravenous injections of typhoid vaccine in acute arthritis was discussed. In the present study, we have confined ourselves to the determination of the value of foreign protein in the treatment of the more obstinate chronic cases of arthritis. The observations contained in this paper cover a period of four years, and during that time we have endeavored to find answers to a number of important questions relative to this subject.

We have attempted to determine whether it is possible to actually and permanently cure cases of chronic arthritis by this method of treatment, or whether, in the absence of a cure, it is possible to improve the patient's condition without at the same time doing him harm. In using the word "cure" we wish to convey the meaning of decided improvement of motion, and cessation of arthritic pain.

During the past four years, we have had charge of seventy cases of chronic arthritis. Of these, sixty were hospital cases, and ten were private cases. We have had three presumable cures in the hospital cases, and three in private practice. Of the hospital cases, one patient has been free from arthritic symptoms for three years and two patients have been symptomless for two years; of the private cases, two patients have been free from arthritic symptoms for two years and one patient for fifteen months. These cases have not been observed for a sufficiently long time to make us certain that the cure has been permanent, but their condition is, up to date, most satisfacory. All of the six patients mentioned as cured are working at present, and earning their living, whereas, previously, they had been helpless invalids. Two of the patients still have a slight amount of deformity due to the presence of firm bands of adhesions and bony changes in the joints. One could hardly expect foreign protein to alter firm fibrous adhesions or bony changes in and around the involved joints. Undoubtedly, the violent shaking of all the joints during the chill following the administration of the protein causes the breaking up of numerous fine adhesions in the joints and their associated tendinous sheaths. The degree of

* From the First Medical Division, City Hospital.

1. Snyder, R. G.: A Clinical Report of Nonspecific Protein Therapy in the Treatment of Arthritis, Arch. Int. Med. **22**:224 (Aug.) 1918.

improvement in these cases is, in part, due to the breaking up of these fine adhesions and release of muscle spasm following relief from pain.

The average percentage of cures in this series of chronic arthritis was about 8.5. In reviewing them, we have been impressed by the fact that all our "cures" occurred in patients who had suffered from arthritic symptoms for less than two years.

It would appear that the improvement in these cases was directly due to the foreign protein therapy, as they all had previously been given the routine treatment for chronic arthritis without any definite improvement in their symptoms. The routine treatment consisted of application of various liniments to the joints, rest in bed, the removal of all apparent foci of infection, special diets, and baking.

Of the patients who were only improved, the majority had suffered from arthritis for several years. In many instances, their joints showed well marked deformities and bony changes. The degree of benefit to be obtained varies with the individual case, and is nearly always greatest in the joints of the upper extremities. Here 50 per cent. showed considerable improvement in motion and decrease in pain. In the joints of the lower extremities, the results are not so good; only 25 per cent. of these cases showed slight improvement in motion and pain. However, as these patients are, as a rule, helpless invalids, they are usually extremely grateful for any improvement, no matter how slight.

The intravenous foreign protein treatment is contraindicated in cases of chronic arthritis complicated by any form of tuberculosis, extreme emaciation from any cause, cardiac decompensation and excessive hypertension.

The size of the dose is always an important question to be decided. Large doses which produce a marked febrile reaction and a very severe chill cannot be given without a corresponding risk to the patient. Several deaths are known to have occurred as a result of too large doses. In order to minimize this danger, we have tried to determine whether the beneficial results obtained were due to the production of the chill or to the size of the dose of foreign protein. After considerable experimentation, it became apparent that the chill is the important guiding factor, consequently there is no advantage in increasing the dose of protein with each injection. If the initial dose is large enough to produce a chill, it is not necessary to increase the dose as long as it continues to give a satisfactory reaction. In our series, the dose used was ten million typhoid bacilli, or from ½ to 1 grain of secondary proteose.[2]

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2. The secondary proteose employed in this series of cases was prepared from milk, and was obtained through the courtesy of the Arlington Chemical Company.

Most of the patients with chronic cases are poorly nourished, and the injection should, therefore, be given only once a week to prevent rapid loss of weight. Since each injection should be preceded by thorough catharsis and is usually followed by nausea for several hours, each treatment means almost twenty-four hours of complete abstinence from food. By observing the precautions in regard to the contraindications, the size of the dose and the interval between injections, none of our patients showed any ill effect. Some of the patients had as many as from fifty to seventy-five injections of foreign protein.

The foreign protein most commonly used in this country has been typhoid vaccine, on account of its accessibility; the dose is estimated by the number of bacilli injected. The use of any vaccine as foreign protein for intravenous use has certain disadvantages—for instance:

1. The dose is uncertain, inasmuch as bacterial counts in vaccines are only approximate,[3] and the protein content of different types of bacteria is variable.[4]

2. The introduction into the circulation of endotoxins in large quantities is to be avoided, if possible. Since all vaccines contain both protein and endotoxins, the elimination of endotoxins as a dangerous factor can only be accomplished by the use of secondary proteose.

3. There is always a slight danger of introducing live organisms into the circulation even when the vaccines are prepared in the most reliable laboratories.

4. All bacteria contain potentially both primary and secondary proteoses and it has been shown that the primary are more toxic than the secondary proteoses.

Osborne and Wells[5] have shown that it is impossible to produce anaphylactic shock by the use of secondary proteose. Since fatalities have been known to occur, following the intravenous administration of large doses of typhoid vaccine, we believe that the presence of primary proteose in the vaccine is in all probability a source of constant danger. The primary proteose may be present in the vaccine used, as a result of autolysis, or may be liberated in the circulation after inoculation, as a result of the natural splitting of the bacterial protein molecule.

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3. McCoy, G. H.: Hygienic Laboratory Bulletin No. 110.

4. Vaughn, Victor C.: Poisonous Proteins, St. Louis, C. V. Mosby Company.

5. Osborne and Wells: The Anaphylactic Reaction with So-Called Proteoses of Various Seeds. The Biological Reactions of the Vegetable Proteins, J. Infect. Dis. **17**:259 (July) 1915.

SUMMARY

The majority of the patients in this series have at one time or another during the past three years had both typhoid vaccine and secondary proteose administered intravenously. They have experienced less nausea, headache and weakness following the use of secondary proteose than after the injection of typhoid vaccine. Over a long series of injections they seem to lose less weight with the use of secondary proteose than with the typhoid vaccine. On the whole, the proteose appears to be less toxic, and it is of significance that patients who have been treated with both typhoid and proteose strongly prefer the proteose for subsequent injections.

In relieving the pain and in improving the motion in the joints, equally good results seemed to follow the use of proteose and typhoid vaccine.

Cases of chronic arthritis which have not been relieved by the routine treatment consisting of sodium salicylate, acetylsalicylic acid, colchicin, cincophen, hot packs, baking or massage are, as a rule, materially benefited by the intravenous administration of small doses of foreign protein. The degree of benefit to be obtained varies with the individual case, and is nearly always greatest in the joints of the upper extremities.

The writers are indebted to Drs. Bastedo, McCabe, Quinby, Shelby, Brooks, Whitman and Bradbury for the use of cases in compiling this article.

RENAL GLYCOSURIA *

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While the majority of clinicians have admitted the existence of renal glycosuria, the number of entirely acceptable cases that have been reported is small. Allen [1] accepts only two, those of Bönninger [2] and Tachau,[3] and Foster [4] found no others above suspicion. Recently, several cases have been reported, some of which present the characteristics of mild diabetes mellitus. With the introduction of simple, accurate methods for determining the sugar content of the blood, it has been possible to establish the diagnosis on a firm basis.

The subject has been discussed in detail by several modern authors, notably Goto,[5] Bailey [6] and Lewis and Mosenthal.[7] It is important to remember that extreme caution should be used in making the diagnosis of renal glycosuria, rather than that of diabetes mellitus; the disastrous injustice of assuring a diabetic that he has the innocuous disease that the former seems to be, and of failing to regulate his diet, is apparent. The diagnosis depends on: (1) glycosuria without hyperglycemia; (2) little, if any, relationship between the amount of sugar excreted and the amount of carbohydrate ingested, and (3) the absence of diabetic symptoms. To these Strouse [8] adds: (4) that the patient must not subsequently develop diabetes mellitus, or show a disturbance of carbohydrate metabolism similar to that found in diabetes mellitus.

It is obvious that the abnormal substance in the urine must be shown to be glucose. It is also important, as pointed out by Bailey,[6] that the urine and blood be collected simultaneously, to make it certain that the glycosuria actually occurs without hyperglycemia. In the case reported by Murlin and Niles,[9] for example, the urinary specimens were collected throughout the day and the blood sugar

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* From the Department of Internal Medicine, Medical School, University of Michigan.

1. Allen, F. M.: Diabetes and Glycosuria, Boston, 1912.
2. Bönninger, M.: Beitrag zur Frage des Nierendiabetes, Deutsch. med. Wchnschr. **34**:780, 1908.
3. Tachau, H.: Beitrag zum Studium des Nierendiabetes, Deutsch. Arch. f. klin. Med. **104**:448, 1911.
4. Foster, Diabetes Mellitus, Philadelphia, 1915, p. 156.
5. Goto, K.: Alimentary Renal Glycosuria, Arch. Int. Med. **22**:96 (July) 1918.
6. Bailey, C. V.: Renal Diabetes, Am. J. M. Sc. **157**:221, 1919.
7. Lewis, D. S., and Mosenthal, H. O.: Renal Diabetes, Bull. Johns Hopkins Hosp. **27**:133, 1916.
8. Strouse, S.: Renal Glycosuria, Arch. Int. Med. **26**:768 (Dec.) 1920.
9. Murlin, J. R., and Niles, W. L.: Renal Glycosuria, Am. J. M. Sc. **153**: 79, 1917.

determinations were made five hours after breakfast, at the time when many mild diabetics might well have a normal glycemia. The relationship between the intensity of the glycosuria and the diet varies somewhat in the cases recorded; in some cases, the two were entirely independent; in others, the changes in the former were in the same direction as changes in the latter, but not proportional to them. The absence of diabetic symptoms would seem to be the most important factor in the diagnosis, and yet some observers have accepted as examples of renal glycosuria cases in which there were definite symptoms of the graver disorder. The patient of Murlin and Niles [9] had a history of furunculosis, polyuria, thirst and loss of weight. Galambos' patient [10] had polyuria and polydipsia. Only a few cases were under observation for a sufficient length of time to warrant any opinion concerning the possible evolution into diabetes mellitus; chief among these are those of Boenninger,[2] Graham,[11] Paullin,[12] Goto,[5] Garrod [13] and Strouse.[8]

Because of the paucity of our knowledge of this remarkable anomaly, it seems desirable to add our observations to those already found in the literature. This case is of especial interest because of the enormous quantities of sugar excreted.

REPORT OF CASE

The patient (No. 20-658), a married negress, 24 years of age, entered the hospital Oct. 14, 1920, with several indefinite complaints, chiefly pain in her right chest.

Family History.—Her father died at the age of 41 of "kidney trouble" and her mother at the age of 39 of "heart trouble with dropsy." Four brothers and three sisters are in good health; there is no history of familial disease, and she knows of no one in her family who had diabetes.

Previous History.—She was married at the age of 22, and her husband is in good health. She has never been pregnant. She had measles, mumps and chickenpox in childhood, with good recoveries from all three. For two months at the age of 12, she had attacks of sharp pain in both chests. Throughout her life she had frequent attacks of tonsillitis, with quinsy five years ago; her tonsils were removed three years ago. Her teeth have caused her a great deal of trouble. Headaches have been common and severe.

She admits having had sexual intercourse since the age of 15, but denies gonorrhea and syphilis, and gives no history suggestive of either, except an operation for "appendicitis" at the age of 16, since when she has not menstruated. Her appetite has always been good, but never unusual. For the past five months she has had some nocturia but no polyuria.

January, 1920, she had influenza, followed by pneumonia. At this time she was in bed for about three months, with a severe cough, a moderate irregular fever and considerable sputum, which was frequently dark colored but never

10. Galambos, A.: Ueber den renalen Diabetes, Deutsch. med. Wchnschr. **51**:1792, 1914.

11. Graham, G.: Variations in the "Leak Point" in Diabetes. I. A Low Level, J. Physiol. **49**:46 (Proc.) 1915.

12. Paullin, J. E.: Renal Glycosuria, J. A. M. A. **75**:214 (July 24) 1920.

13. Garrod, A. E.: Brit. M. J. **2**:850, 1913.

red. Associated with this illness, and persisting to the present time, she has had recurring attacks of sharp, shooting pain in her lower right chest, worse on inspiration, and entirely absent during the intervals. She believes that during the month after she was allowed out of bed she had a slight afternoon fever, and she has had drenching night sweats two or three times a week. There is no cough at present. During the attack of pneumonia, her left ankle became red, swollen and painful; the redness and swelling disappeared, but she still complains of soreness. There have also been occasional attacks of sharp, shooting pains in the legs and left arm, coming chiefly at night, and lasting only a few minutes. For the last five or six months she has been troubled by palpitation of the heart and shortness of breath on moderate exertion. Before she had pneumonia, she weighed 139 pounds; after getting out of bed, she weighed 112; her present weight is 122.

Physical Examination.—On examination, the patient was found to be a slender, fairly well nourished young negress, lying comfortably on the examination table, in no apparent pain or discomfort. She was mentally alert, and answered questions promptly and intelligently. Physical examination revealed no important evidence of pathology. Her teeth were in very poor condition, and many were carious. Careful examinations of her chest by several members of the staff were entirely negative. There were a few firm, painless inguinal glands felt on each side. Her fundus was reported from the department of ophthalmology as practically normal.

Blood.—Hemoglobin, 90 per cent. on the Talquist scale; red blood cells, 5,000,000; leukocytes, 8,400, of which 61 per cent. were polymorphonuclears, 13 per cent. small lymphocyes, 20 per cent. large lymphocytes and 6 per cent. large mononuclear cells. Blood pressure was 115 systolic, and 65 diastolic.

Urine.—Urine was pale yellow, slightly cloudy, and acid; specific gravity, 1.050; no albumin, a few epithelial cells, and oxalate crystals; a drop of it reduced Fehling's solution rapidly and completely; the ferric chlorid reaction was negative.

Two determinations of blood sugar on the day of admission were 0.090 and 0.091, respectively.

Roentgenologic examination of chest was entirely negative.

Clinical Course.—During her stay in the hospital she was afebrile, except during an attack of acute intestinal obstruction. Her pulse rate varied between 80 and 100, and her respiratory rate between 20 and 25. She was treated at first as a diabetic, and it was not until several determinations showed that her blood sugar was persistently normal, and after her heavy glycosuria had persisted through several days of a low carbohydrate diet, that a serious doubt as to the diagnosis of diabetes mellitus was entertained. The study of the sugar content of her blood and urine after the ingestion of glucose was convincing evidence that it was not a case of typical diabetes.

The substance in the urine was found not only to reduce Fehling's solution and Benedict's qualitative reagent, and to give a satisfactory endpoint with Benedict's quantitative solution, but it also gave the other important reactions of glucose. It was fermented rapidly by yeast, with the production of gas; there was no gas production by the yeast in the control urines. Typical phenolhydrazine crystals were thrown down by the Kowarski method. Polarized light was rotated to the right, and glucose estimations by the polariscope agreed closely with those by Benedict's reagent.

Urinary glucose was determined throughout the study by the Benedict method and the blood sugar by Benedict's modification of the Lewis-Benedict method.

Comment.—The relation of her urinary sugar excretion to her diet is shown in Table 1. During the periods of observation, she was on six dietary regimes. From October 5 to October 20, inclusive, she

TABLE 1.—Relation of Diet to Urinary Sugar

Date	Diet				Blood Sugar, per Cent.	Urine			Remarks
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories		Amt., C.c.	Sp. Gr.	Glucose, Gm.	
10/15	20	84	13	890	0.090	.....	1.050	+	Single specimen
10/16	19	100	16	1,043	.....	.....	1.039	+	Low protein
10/17	20	74	15	807	.....	1.120	1.039	43.2	Low carbohydrate diet
10/18	20	83	15	884	0.090	950	1.042	36.0	
10/19	22	92	12	967	.....	1.030	1.043	41.1	
10/20	15	73	15	782	0.100	960	1.038	44.9	
10/21	100	137	331	2,960	.....	1,720	1.038	57.7	Unrestricted diet
10/22	119	85	356	3,069	.....	1,085	1.044	67.8	
10/23	98	117	287	2,596	.....	1.285	1.047	57.1	
10/24	113	116	332	3.020	.....	1,750	1.040	87.9	
10/25	18	16	161	480	0.080	1.320	.....	44.8	Plus 100 gm. glucose
10/26	127	142	341	3,147	.....	960	1.050	47.0	
10/27	98	118	291	2,621	.....	2,610	1.022	43.0	Fluid intake, 5,000 c.c.
10/28	87	101	282	2,368	.....	1,250	1.045	59.6	Fluid intake, 1,000 c.c.
10/29	133	125	381	3,225	.....	995	1.043	58.3	
10/30	182	127	374	3,488	.....	1,840	1.034	57.5	
10/31	168	51	221	2.016	.....	1,000	1.042	61.7	
11/ 1	92	84	131	1.740	.....	1,365	1.041	58.3	
11/ 2	76	88	91	1.360	.....	1,000	1.038	41.7	
11/ 3	147	65	223	2,073	.....	1,220	1.043	75.0	
11/ 4	63	89	87	1,400	.....	1,070	1.050	60.9	
11/ 5	87	55	93	1.215	.....	850	1.045	51.8	
11/ 6	102	47	163	1.571	0.076	1,060	1.044	59.9	
11/ 7	157	106	298	2,776	.....	2,140	1.028	63.9	
11/ 8	90	74	189	1,821	.....	1,195	1.042	62.9	
11/ 9	101	65	89	1.353	.....	2,411	.....	53.6	Plus 100 gm. glucose
11/10	138	82	269	2,370					
11/11	122	105	189	2.289	.....	725	1.045	51.8	
11/12	102	145	289	2.846	.....	1,055	1.048	74.2	
11/13	111	122	336	2,891	.....	710	1.043	57.2	
11/14	89	101	291	2.429					
11/15	101	141	336	3.018	.....	1,365	1.050	98.9	
11/16	83	81	241	2.029	.....	1.300	1.048	104.8	
11/17	91	77	262	2,092	.....	1,794	.....	72.4	
11/18	112	116	321	2,774	0.090	875	1.045	56.8	
11/19	52	143	34.2	1.638	.....	1,200	1.040	63.2	Low protein, low carbohydrate diet
11/20	47	179	35.9	1.873	.....	1,130	1.039	50.0	
11/21	47	179	18.2	1.880	.....	1.097	1.040	61.6	
11/22	41	176	34.4	1.889	.....	1,265	1.040	67.9	
11/23	51	197	33.5	2,126	.....	1.533	1.037	67.7	
11/24	55	190	35.5	2,078	.....	1,127	1.043	58.3	
11/25	56	178	34.5	1,969	.....	1.320	1.041	63.3	
11/26	52	169	35.9	1.878	.....	1,150	1.045	82.2	
11/27	55	223	29.7	2.347	.....	1,025	1.038	55.4	
11/28	56	171	31.8	1,884	.....	1,195	1.041	66.4	
11/29	56	192	32.7	2.080	.....	720	1.040	36.9	
11/30	55	204	41.1	2,226	.....	1,030	1.042	56.6	Diuretin, 30 grains
12/ 1	55	184	35.0	2,023	.....	1,165	1.040	64.9	Diuretin, 90 grains
12/ 2	57	223	29.7	2,353	.....	850	1.033	31.8	Diuretin, 90 grains
12/ 3	59	161	33.0	1,815	.....	1 200	1.041	61.3	Diuretin, 90 grains
12/ 4	56	216	32.4	2,297	.....	1,380	1.036	52.8	Diuretin, 90 grains
1/11	58	124	255	2,376	.....	410	1.048	26.3	
1/12	55	115	235	2,195	.....	1,145	1.046	74.2	
1/13	57	129	233	2,320	.....	530	1.050	36.8	
1/14	58	143	256	2.540	.....	360	1.033	19.8	
1/15	58	130	253	2.415	.....	620	1.045	48.4	
1/16	57	144	253	2,545	.....	390	1.044	27.5	
1/17	56	105	232	2,100	.....	1,235	1.040	77.2	
1/18	48	169	234	2,190	.....	520	1.045	36.6	
1/19	59	104	213	2.025	.....	490	1.050	40.9	
1/20	56	114	196	2,035	.....	365	1.040	15.7	
1/21	46	61	219	1,610	.....	920	1.038	51.1	
1/22	49	128	187	2.095	.....	705	1.043	44.1	100 gm. glucose added to diet in divided doses
1/23	76	144	258	2,630	.....	470	1.041	30.1	
1/24	46	120	234	2.200	.....	2.330	1.037	122.6	
1/25	74	136	257	2,550	.....	670	1.039	37.2	
1/26	63	127	248	2,385					
1/27	68	141	258	2,675	.....	870	1.040	41.2	
1/28	65	128	267	2.380	.....	820	1.039	38.7	
1/29	66	147	265	2,640	.....	930	1.038	38.1	
1/30	72	133	254	2.400	.....	780	1.039	28.9	
1/31	69	127	244	2,395	0.090	630	1.043	41.1	
2/ 3	0	0	0	0	.....	1,200	1.033	72.3	Starvation
2/ 4	0	0	0	0	.....	1,155	1.036	46.6	N., 6.352 gm.
2/ 5	0	0	0	0	.....	970	1.042	61.4	N., 4.266 gm.
2/ 6	0	0	0	0					
2/ 7	0	0	0	0	.....	875	1.032	39.3	N., 3.313 gm.
2/ 8	0	0	0	0	.....	1,080	1.031	36.5	N., 4.536 gm.

was on the diet which we routinely give patients with diabetes mellitus to reduce their hyperglycemia, and which contains approximately 15 gm. carbohydrate per day. From October 21 to November 18 her diet was not restricted, and her daily carbohydrate intake varied from 85 to 350 gm. During the third period, from November 19 to December 4, she was on a low protein, low carbohydrate diet with a daily carbohydrate intake varying less than 5 gm from 55 gm. From January 14 to January 21, she was on a diet containing about 240 gm. of carbohydrate. During the following ten days the diet was not changed from that of the fourth period, except that 100 gm. glucose were added daily, in three doses. Finally, she was starved for six days.

It is apparent that the amount of glucose in the urine had no relation to the amount of carbohydrate ingested, and that, while the variation in the glycosuria from day to day was large, it was not dependent on the diet. It is especially interesting to notice that the addition of 100 gm. glucose to the intake did not increase the glycosuria, while complete starvation did not decrease it.

TABLE 2.—Response of Blood and Urine to 100 Gm. Glucose by Mouth

Time	Water Ingested, C.c.	Blood Sugar, per Cent.	Urine					Average Normal Blood Sugar, per Cent	Typical Diabetic Blood Sugar, per Cent.
			Quantity, C.c.	Specific Gravity	Glucose, Gm.	Per Cent.	Per Hour, Gm.		
Fasting	400	0.071	74.0	1.044	4.1	5.5	2.3	0.078	0.11
15 minutes	...	0.087							
30 minutes	400	0.092	46.0	1.044	2.8	6.1	5.6	0.108	0.15
1 hour	200	0.090	65.5	1.040	4.1	6.4	8.2	0.088	0.24
2 hours	200	0.043	342.0	1.014	6.4	1.9	6.4	0.083	0.20
3 hours	200	0.048	523.0	1.008	4.6	0.9	4.6	0.078	0.30
5 hours	...	0.068	197.0	1.020	3.8	2.0	1.9		

Her reaction to ingested glucose was studied in both the urine and the blood. The patient was given 100 gm. of glucose by mouth while she was in a fasting state in the morning. Sufficient water was given during the test to assure the collection of urinary specimens. The results are shown in Table 2. To the table, for convenience, is added a normal blood sugar curve, and a blood sugar curve of a diabetic, both taken from Strouse.[14] In this connection it will also be noted in Table 1 that the daily ingestion of 100 gm. glucose added to the diet in divided doses had no effect on the amount of sugar in the urine.

The effect of diuresis was studied in three experiments. During one of the days when the patient was on an unrestricted diet, she was asked to drink 5,000 c.c. of fluid; on this day her sugar excretion was 43 gm. On the following day, her intake was limited to 1,000 c.c., and her glucose output was 59.6 gm. This difference is within the limits of variation in her glycosuria when there was no apparent change in

14. Strouse, S.: Alimentary Hyperglycemia, Arch. Int. Med. **26**:759 (Dec.) 1920.

the conditions. On another occasion, while fasting, she was given water in the same amounts and at the same intervals as during the study of the effect of 100 gm. glucose, that is, 400 c.c. at the start of the experiment, 400 c.c. at the end of thirty minutes, and 200 c.c. each at the end of the first, second and third hours. The results are presented in Table 3. It will be noted that the rate of glucose excretion remained practically constant, though the percentage of urinary glucose varied inversely with the diuresis. It will also be noted that the rate was practically the same as the average throughout her stay in the hospital; 60 gm. a day is at the rate of 2.5 gm. per hour. In the third experiment an effort was made to promote diuresis by oral administration of 90 grains theobromin sodium salicylate (diuretin) daily. This drug by mouth is also known to cause glycosuria.[15] In this case, as in that of de Langen [16] neither diuresis nor increase in the glucose excretion was noted.

TABLE 3.—Response of Urine to Water by Mouth

Time	Water Ingested, C.c.	Urine				
		Quantity, C.c.	Specific Gravity	Glucose, Gm.	Per Cent.	Per Hour, Gm.
Fasting	400					
30 minutes	400	108.0	1.041	6.8	6.3	2.4
1 hour	200	24.0	1.040	1.3	5.4	2.6
2 hours	200	215.0	1.010	2.2	1.0	2.2
3 hours	200	366.0	1.010	2.7	0.7	2.7
5 hours	...	72.0	1.034	3.3	4.6	1.7

From the time when Klemperer [17] first declared the existence of renal glycosuria, much interest has been centered on the state of the kidney function in the cases. Klemperer insisted that it is characteristic of the affection that when nephritis develops, the glycosuria disappears. Other observers, on the contrary, have believed that renal glycosuria is a part of nephritis. Lüthje [18] claimed such a relationship, because his patient was apparently free from sugar before the development of nephritis, and developed glycosuria shortly after nephritis. Naunyn [19] also upheld this view, and reported three cases in nephritics; there were no blood sugar determinations in his data, however, and the diagnosis of renal glycosuria is not established. Tauchau's patient [3]

15. Nishi, M.: Ueber den Mechanismus der Diuretinglycosurie, Arch. f. exper. Path. u. Pharmakol. **61**:401, 1909.

16. de Langen, C. D.: Beitrag zur Kasuistik des renalen Diabetes, Berl. klin. Wchnschr. **51**:1792, 1914.

17. Klemperer, G.: Ueber regulatorische Glycosuria und renalen Diabetes, Berl. klin. Wchnschr. **33**:571, 1896.

18. Lüthje, H.: Beitrag zur Frage des renalen Diabetes. München. med. Wchnschr. **38**:1471, 1901.

19. Naunyn, B.: Der Diabetes Mellitus, Wien., 1906, p. 136.

had a transient acute nephritis. Both of the cases reported by Bailey [6] gave evidence of nephritis. In the majority of the cases, however, renal function was not definitely impaired.

The urine of our patient frequently showed a trace of albumin, but casts were found at no time. The urea content of her blood was determined on two occasions, during the period when she was on an unrestricted diet, and found to be 36 and 40.8 mg. per 100 c.c., respectively. Phenolsulphonephthalein, injected intramuscularly, was recovered in the urine to the extent of 65 per cent. in the first hour and 20 per cent. in the second; on repetition several days later, 63 and 14 per cent., respectively, were recovered. No evidence of nephritis could be obtained.

The nitrogen determinations on the urine of the starvation period raise some interesting but unanswerable questions. The values given were determined by Folin's micro-Kjeldahl method and checked by the original Kjeldahl method. These figures, which are presented in

TABLE 4.—URINARY GLUCOSE AND NITROGEN DURING STARVATION

Date	Glucose, Gm.	Nitrogen, Gm.	D : N
2/3	72.3		
2/4	46.6	6.352	7.33 : 1
2/5	61.4	4.268	14.38 : 1
2/6	.....	.....	.....
2/7	39.3	3.313	11.86 : 1
2/8	36.5	4.536	8.05 : 1
Average	45.9	4.61	9.66 : 1

Table 4, gave a D:N ratio of about 10:1. It seems safe to assume that on the sixth day of starvation the glycogen deposits of the body have been exhausted, and we have no evidence in support of the view that fat is converted into glucose. Yet it is hard to believe that all this sugar was derived from protein.

December 9, she complained of diffuse abdominal pain. She began vomiting and all efforts toward moving her bowels failed. Her abdomen was rigid throughout. A diagnosis was made of intestinal obstruction and she was transferred to the Surgical Clinic for operation. At operation, adhesions were found about her colon, with a sharp kinking of the intestine. Her uterus, tubes and right ovary were found to have been removed; the left ovary was in place. The adhesions were separated and the intestine freed. She returned from the operating room in good condition and made an uneventful recovery. The wound healed rapidly, and there were never any symptoms of acidosis.

SUMMARY

A case of renal glycosuria is described. During a period of four months the patient excreted an average of 60 gm. glucose daily with

a variation of from 15 to 122 gm. The amount was not related to the carbohydrate intake. After the ingestion of 100 gm. glucose, the blood sugar rose from a fasting per cent. of 0.071 to 0.092 in thirty minutes; by the end of two hours it had fallen to 0.043 per cent, and after five hours it was found to be 0.068 per cent. Even with a blood sugar as low as 0.043 per cent., glucose was excreted at the rate of over 5 grams per hour. Diuresis by increased water ingestion caused no increase in the glycosuria, and no effect was seen from the administration of diuretin in large doses. No evidence of nephritis was found. The D: N ratio in the urine of starvation was about 10: 1. She reacted to a laparotomy for acute intestinal obstruction in a perfectly normal manner.

I wish to thank Dr. L. H. Newburgh for his kind and helpful suggestions in this study.

THE RIGHT VENTRICLE IN PULMONARY TUBERCULOSIS *

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Current medical opinion, in so far as it is directed to the heart in the tuberculous patient, seems to take it for granted that in chronic phthisis there is frequently found a dilatation and hypertrophy of the right ventricle. This is explained usually by the assumption that with extensive pulmonary disease there is a partial obliteration and obstruction of the pulmonary stream bed which exacts an increased amount of work from the right ventricle to maintain the circulation. This mechanism would be analogous to the left ventricular hypertrophy that accompanies arterial hypertension. Thus Bohland [1] states that such a hypertrophy is present in chronic phthisis, that it is compensatory in its nature, and that the enlarged right ventricle, having little reserve, easily becomes insufficient. Krehl,[2] too, mentions that such hypertrophy is of frequent occurrence.

On analysis, the evidence for this belief is found to be conflicting and for the most part inadequate. Portal [3] in 1792, concluded, on the basis of necropsy studies, that the right auricle and ventricle dilate in chronic phthisis because of obstruction of the pulmonary blood flow. Laennec, Grissole, Louis, Rokitansky and Rigal, on the other hand, state that dilatation of the right heart in tuberculosis occurs only exceptionally. Potain [4] noted that the heart of the phthisical patient was usually small, and believed that this was due to the cachexia which accompanies the disease. In those patients in whom the progress of the emaciation was very slow, however, large hearts were often found, which enlargement, Potain thought, was usually due to extrapulmonary causes. Regnault,[5] too, found a true or an apparent hypertrophy of the heart in the majority of cases of fibroid phthisis. He believed that it was caused by complications which acted directly on the heart and delayed the evolution of the tuberculosis with its accompanying cachexia. Dilatation of the right heart, particularly of the auricle, he claimed could be demonstrated quite frequently among

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*From the Montefiore Hospital for Chronic Diseases.
* Read before the Section of Medicine of the New York Academy of Medicine, Feb. 15, 1921.

1. Bohland, K.: Handbuch der Tuberkulose, First Half **4**: p. 5.
2. Krehl, L.: Pathologische Physiologie, Ed. 7, p. 30.
3. Portal, A.: Observations sur la Nature et le Traitement de la phthisie pulmonaire, Paris, 1792.
4. Potain: Le Cœur des Phthisiques, 1892.
5. Regnault, E.: Le Cœur chéz les Tuberculeux, Paris, 1899.

living tuberculous patients by percussion, but more rarely was this shown at necropsy. Regnault believed that emphysema, pleural adhesions, sclerosis and caseation of the lungs, all tending to obstruct the pulmonary blood bed were the cause of this hypertrophy. A number of other authors have arrived at similar conclusions, although they have not clearly differentiated hypertrophy from dilatation. Among these may be mentioned Bard, Decroix, Marucheau, Fraentzel and Buhl.[6]

Two physiologic studies throw some light on this question. In 1876 Lichtheim [7] published an excellent monograph on the physiology of the pulmonary circulation. A brief summary of his conclusions will be illuminating. He first discusses the conventional views on the disturbances of the pulmonary circulation. These had been based on the assumption that a partial obstruction of the lesser circulation, by narrowing the blood bed, prevented the right ventricle from propelling to the left ventricle the same amount of blood as before. Under such circumstances, the left ventricle received an inadequate amount of blood, the arterial blood pressure fell, and the right ventricle became overfilled. To establish equilibrium, the right ventricle had to work harder and eventually hypertrophy. Then the velocity flow in the pulmonary circulation rose until the amount of blood passing through the pulmonary stream bed per unit of time was normal. On this basis were explained the venous stasis, the small pulse, the low blood pressure and oliguria found in pulmonary embolism and in acute pleural effusions. Lichtheim attempted to verify experimentally this theoretical explanation of the mechanism of cardiac response to disturbances of the pulmonary circulation. He found that ligation of the left pulmonary artery had no effect on the arterial blood pressure nor on the heart rate, and that a variation in the carotid pressure did not affect the pulmonic pressure. His final conclusions, drawn from a long series of carefully executed experiments, are: 1. After closure of parts of the pulmonary stream bed the total amount of blood that courses through the remaining vessels is the same as formerly passed through the intact pulmonary circulation. 2. This is accomplished by a rise in pressure in the remaining, i. e., open, pulmonary arteres, together with an increased velocity of flow and a stretching of the arterioles. 3. This mechanism adequately maintains the circulation if not more than three quarters of

6. Bard: Thèse de Lyon, 1879. De la phthisie fibreuse chronique. Decroix: Atrophie du cœur et dilatation des cavités droites dans la tuberculose pulmonaire, Thèse de Paris, 1880. Marucheau: Etat du cœur droit dans la phthisie pulmonaire, Thèse de Paris, 1871. Fraentzel, O.: The Idiopathic Enlargements of the Heart, Wood's M. & S. Monographs, May, 1890, p. 523. Buhl: Messungen der Herzventrikel und der grossen Gefässe, Stuttgart, 1878.

7. Lichtheim, L.: Die Störungen des Lungenkreislaufs und ihr Einfluss auf den Blutdruck, Berlin, 1876. (Hirschwald.)

the pulmonary blood bed is shut off. If the closure exceeds this figure, in spite of the high pulmonic pressure the blood supply to the left heart fails and the arterial pressure drops. The effect that this compensatory process will have on the right ventricle will vary with the extent of the narrowing of the stream bed of the lungs. At first, the dilatation of the arterioles will offset the narrowed blood bed, but with more extensive obstruction of the pulmonary vessels, the right ventricle will be called on for more work to maintain the minute volume flow in the lungs, and will dilate and eventually hypertrophy. The rise in pressure in the pulmonary artery clearly indicates that the right chamber of the heart is working under a greater load.

There are still other factors which determine the effect that diseases of the lung will have on the heart. The most important of these is the elasticity of the lungs which is ably discussed by Bäumler.[8] He recalls that because of the elasticity of the lungs the external pressure on the heart and blood vessels of the mediastinum is less than atmospheric. Within the lungs, and in the rest of the body, however, the pressure is equal to one atmosphere. Thus the flow of the venous blood into the heart, and of the pulmonary blood into the left auricle is aided by this difference of pressures. Extensive pleural adhesions, he says, impair the elasticity of the lungs and prevent the operation of this factor, and are as potent as obstruction of the pulmonary blood bed in increasing the work of the right ventricle and in inducing hypertrophy. It must be remembered, however, that while this negative intrathoracic pressure aids the flow of blood from the lungs to the left auricle, it hinders the flow of blood from the right ventricle to the lungs to exactly the same degree, and that, therefore, a change in this intrathoracic pressure will not alter the total work done by either chamber of the heart. Another element must, however, be taken into consideration. The increased amount of connective tissue which is found in the lung with massive adhesions will impair the elasticity of the lung tissue and will have an effect on the pulmonary vessels which may be analogous to arteriosclerosis in the larger circulation. Such an indirect impairment of the elasticity of the pulmonary vessels will increase the work of the right heart.

The clinical experience of a number of men gives support to this theory. Morgagni[9] described cases in which the necropsy revealed pleural adhesions associated with hypertrophy of the right heart.

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8. Baümler, Ch.: Ueber Obliteration der Pleurasäcke und Verlusst der Lungenelasticität als Ursache von Herzhypertrophie, Deutsch. Arch. f. klin. Med. **19**: 471.

9. Morgagni: Quoted from Grau-Ronsdorf, Internat. Centralbl. f. Tuberkuloseforschung **5**:283, 1910.

Traube,[10] in 1866, presented several necropsy protocols of patients with extensive pleural adhesions and secondary hypertrophy of the right ventricle. Du Castel,[11] in a study of fifteen cases of tuberculosis, found right ventricular hypertrophy only if pleural adhesions or pulmonary sclerosis were present. Palhier [12] describes cases in which the postmortem examination showed dilatation of the right heart, associated with pleural adhesions and emphysema, and it is to these factors, rather than to a restriction of the blood bed that he attributes the change. On the other hand, Lienart,[13] who reports dilatation of the right heart in two thirds of his cases of phthisis, ascribes the cause to a diminution of the blood bed from fibrosis and emphysema. Sokolowski [14] cites several necropsies of patients with fibroid phthisis in whom he found enlarged right hearts.

All of these clinical and pathologic reports are open to the criticism that the methods by means of which the cardiac hypertrophy was determined are not sufficiently accurate. Exact pathologic recognition of hypertrophy of one or both chambers of the heart demands a painstaking dissection and weighing of the organ according to the method of Müeller. A search through the literature reveals only three investigators who have employed this technic in the study of the heart of the tuberculous. Hirsch [15] studied 120 cases of tuberculosis, in 35 per cent. of which he discovered a marked right ventricular hypertrophy. The degree of hypertrophy paralleled the extent of pleural adhesions and of induration of the lung. In acute ulcerative tuberculosis, the heart was small and atrophied. Wideroe [16] found that right ventricular hypertrophy was quite frequent in chronic pulmonary tuberculosis, and that it was the greater, the greater the age of the individual, or the more extensive the lesion. Bret [17] arrived at similar conclusions, but pointed out that the degree of hypertrophy did not always parallel the extent of the lung lesion, nor the duration of the illness.

In view of these findings reported in the literature, and of theoretical considerations which suggested that there was some physiologic basis for the changes that had been described, an electrocardiographic study of a series of tuberculous patients was made in the hope that by this

10. Traube, L.: Gesammelte Beitr. z. Path. u. Physiol. **3**:338, 1866.
11. Du Castel: Récherches sur l'hypertrophie et la dilatation des ventricules du cœur, Arch. Gen. de méd., 7 ser. **5**:25, 1880.
12. Palhier: Contribution a l'etude anatomopath. du cœur dans la phthisis chronique, Thèse de Paris, 1890.
13. Lienart: Dilatation du cœur droit chez les tuberculeux, Thèse de Paris, 1886.
14. Sokolowski, A.: Ueber die fibröse Form der Schwindsucht, Deutsch. Arch. f. klin. Med. **27**:443, 1885.
15. Hirsch, V.: Ueber die Beziehung Zwischen Herzmuskel und Körpermuskulatur, Deutsch. Arch. f. klin. Med. **68**:337, 1900.
16. Wideroe, S.: Die Massenverhältnisse des Herzens unter pathologischer Zuständen Christiania, 1911, abstr. from Zentralbl. f. Herz u. Gefässkrankheiten **3**:121, 294, 1911.
17. Bret, J.: Lyon méd. **122**:452, 1914.

means we might be able to determine whether or not there was a predominance of one of the chambers of the heart. At the same time, the case was studied in order to correlate the electrocardiographic with the clinical findings. The material from which this study was made consists of ninety-seven consecutive, unselected cases from the tuberculosis service of the Montefiore Hospital.[18]

The procedure of examination was as follows: The salient points in the history were noted, and then the patient was subjected to a physical examination in which especial attention was directed to the cardiovascular system. The blood pressure was taken, the pulmonary lesion was noted, particularly whether or nqt it was of the fibroid type, and the degree of activity of the lesion was remarked. Electrocardiograms of the patients were taken in the usual way with a Cambridge electrocardiograph and immersion electrodes. The conventional three leads were taken, and the electrocardiograms were interpreted by one of us (Mann) who had no clinical knowledge of the case. Roentgenograms were made of many patients, but they were of little assistance in this study. With extensive lung lesions, the outlines of the borders of the heart are often obscured, and cardiac displacement is very frequent. This makes it very difficult to decide from a plate whether or not there is a slight enlargement of one of the ventricles.

The results do not confirm the views which we held at the outset of this study, but present a number of interesting points. The first fact that stands out is that in relatively few cases is predominance of one chamber or another very marked. The reports usually read, "tendency to left ventricular predominance" or "slight right ventricular predominance." Of the ninety-seven cases, twenty-eight show right, twenty-nine left ventricular predominance, and in forty there was no predominance of either ventricle. Three of the patients exhibiting left ventricular predominance must be excluded from the series because they show definite extrapulmonary causes for left ventricular hypertrophy. Even without them, the frequency of occurrence of right and left ventricular predominance is about equal. An analysis of the clinical features of the cases was made in the attempt to explain this phenomenon.

It is well known that many tuberculous patients give evidence of a mild hyperthyroidism, particularly early in the course of the disease. This is manifested by thyroid enlargement, slight prominence of the eyes, frequently associated with a positive Von Graefe sign, nervousness, tachycardia and vasomotor disorders. With the idea that the left ventricular predominance might be caused by such a thyroid disorder, the patients were grouped into those giving definite symptoms of

18. We are indebted to Dr. Fishberg, director of the service, for permission to study the patients.

thyroid disturbance and those in whom the symptoms were suggestive. Another group was made up of the fibroid cases, and, finally, patients were classed according to the degree of activity of the tuberculous lesion. Table 1 presents the data.

TABLE 1.—VENTRICULAR PREDOMINANCE OF VARIOUS GROUPS OF CASES

	R. V. P.	L. V. P.	Normal*
Definite hyperthyroidism	6	8	9
Possible hyperthyroidism	9	10	9
Fibroid phthisis	10	13	16
Active cases	13	15	22
Inactive cases	15	12	18

* Normal means predominance of neither chamber.
In two cases showing L. V. P., the activity of the lesion was not noted.

These figures give no evidence of correlation between predominance of one ventricle and any of the factors mentioned in the table. But it is possible that in each case several influences may be at play, and that the final effect is the resultant of these components. This suggests a study of some of the individual cases.

Those with fibroid phthisis may be first considered.

REPORT OF CASES

CASE 1 (38893).—J. B., male, aged 32; duration, seven years. Lesion: extensive bilateral fibroid phthisis; inactive. Heart, normal to physical examination. Pulse, full, soft, rate 84. Blood pressure, 95/70. Veins of right neck rather full. No signs of hyperthyroidism. Electrocardiogram, right ventricular predominance.

This case taken by itself shows a definite right ventricular predominance conditioned apparently by a fibrosis of the lung. That the situation is not so simple is shown by Cases 2 and 3.

CASE 2 (44142).—N. K., male, aged 39; duration, one year. Lesion: bilateral cavitation and fibrosis, associated with asthmatic attacks; active. Heart normal to physical examination. Pulse, weak, rate 96. Blood pressure, 106/65. Slight cyanosis. Thyroid not felt, slight Von Graefe sign present. Electrocardiogram, left ventricular predominance.

CASE 3 (38146).—E. B., female, aged 32; duration, four years. Lesion: fibroid phthisis of both upper lobes with asthmatic breathing all over chest; active. Heart normal to physical examination. Pulse, small, soft, rate 124. Blood pressure, 120/74. Slight cyanosis. No signs of hyperthyroidism. Roentgenogram, heart abnormally small. Electrocardiogram, normal.

Clinically these two cases correspond to Case 1, yet in one of them there is left ventricular predominance, and in the other the heart is normal. The cause for this variation is not apparent.

A similar series may be shown to exist in the thyroid cases.

CASE 4 (41424).—B. K., female, aged 22; duration, six months. Lesion: consolidation of the whole right lung; active. Heart small. Roentgenogram, heart abnormally small. Pulse, good quality; rate 140. Blood pressure, 125/70.

Thyroid, moderate general enlargement; von Graefe sign present. Electrocardiogram, left ventricular predominance.

Case 5 (41364).—E. L., female, aged 19; duration, six months. Lesion: infiltration of whole left lung; infiltration with multiple cavities of right upper lobe; active. Heart, displaced a bit to the left. Systolic murmur at pulmonic area. Pulse, good; rate 132. Blood pressure, 108/78. Thyroid isthmus palpable; von Graefe sign present. Roentgenogram, abnormally small heart displaced to the left. Electrocardiogram, right ventricular predominance, not well marked.

Case 6 (39806).—E. K., female, aged 25; duration, two years. Lesion: cavitation and infiltration of left upper lobe; left artificial pneumothorax; infiltration of right upper lobe; active. Heart displaced to left. Pulse, small, weak; rate, 108. Blood pressure, 104/74. Thyroid enlarged. Von Graefe present. Patient is very unstable emotionally. Electrocardiogram, normal.

Here, again, are three cases, almost identical clinically, but presenting absolutely different electrocardiographic findings.

Since the electrocardiogram does not give information as to whether or not hypertrophy has occurred in one or the other of the ventricles, but merely indicates the predominance of one chamber over the other, depending on the relative amounts of their muscle mass, the thought occurs that several factors may be operative in some of these patients: that, for instance, in a case showing both fibrosis and hyperthyroidism, both chambers of the heart may hypertrophy, but their relative muscle mass may remain unchanged. The following cases could be cited in support of this proposition:

Case 7 (39121).—W. S., male, aged 53; duration, five years. Lesion: bilateral extensive fibroid phthisis; inactive. Heart, normal to physical examination. Pulse, good; rate, 104. Blood pressure, 170/95. Slight edema of feet, marked myocardial insufficiency some months ago. Urine shows albumin and casts. No signs of thyroid disorder. Electrocardiogram, normal.

Case 8 (41127).—S. L., male, aged 32; duration, two years. Lesion: extensive bilateral fibrosis; inactive. Heart displaced slightly to the left. Pulse, good; rate, 104. Thyroid isthmus enlarged; von Graefe sign present. Nervous instability. Blood pressure, 104/68. Electrocardiogram, normal.

The interplay of the hypertension and fibrosis in the first instance, and of the slight hyperthyroidism and fibrosis in the second, might account for the normal electrocardiographic complex. But a further study of many individual cases does not bear this out. The different electrocardiographic findings seem to be distributed quite vicariously, and we have been unable to determine any clinical criteria from which we might venture to predict whether there was predominance of either of the ventricles. The activity or inactivity of the pulmonary lesion is not a factor, nor has the duration of the illness any influence (Table 3). If, however, we classify the cases according to sex, an interesting relationship appears (Table 2).

Although the series is not large, the differences are too great to be accidental. To make sure of this point, these and other data were checked up statistically. The striking fact appears that left ventricular predominance is about twice as common in the women as in the men, and that right ventricular predominance is twice as frequent in the men as in the women. It is difficult to find a satisfactory explanation of

TABLE 2.—CLASSIFICATION OF CASES ACCORDING TO SEX

Sex	L. V. P.	R. V. P.	Normal	Total
Female	19	9	20	48
Male	10	20	19	49

this phenomenon. It is suggestive, however, that symptoms of hyperthyroidism were found more than twice as often in the women as in the men. The pulse rates, too, are interesting. Of the forty-eight women, thirty-one had a pulse rate over 110. Of the forty-nine men, only ten had a pulse rate over 110, and in sixteen it was below 90.

A further analysis is detailed in Table 3.

The difference in the ages of the two sexes is accidental. Probably for social and economic reasons, the older women do not enter our hospital so frequently as do the older men. But the significant fact is that in spite of the disparity of the ages in the male and female series, the age distribution of predominance of the ventricles runs parallel in both. Thus, in both sexes right ventricular predominance is found in the youngest, no predominance in the next age group, and left ventricular in the oldest. We have been unable to discover whether this has any particular significance. Such a tendency to predominance of

TABLE 3.—DETAILED ANALYSIS OF CASES

	Male			Female		
	Number of Cases	Average Age, Years	Average Duration, Years	Number of Cases	Average Age, Years	Average Duration, Years
R. V. P.	20	39.0	5.9	9	23.6	2
Normal	19	44.8	4.8	20	29.2	4
L. V. P.	10	48.2	5.2	19	36.5	3.3

the left chamber is, of course, more frequent in the older age groups. It will be noted that the duration of the tuberculosis has no influence on the distribution.

Another fact resulting from this study is that displacement of the heart, which is so common in the tuberculous, and which is often extreme, ordinarily has no effect on the outline of the electrocardiogram.

SUMMARY

1. An electrocardiographic study of ninety-seven patients with pulmonary tuberculosis revealed 29 per cent. with right ventricular pre-

dominance, 30 per cent. with left ventricular predominance, and 41 per cent. with no predominance of either chamber.

2. Right ventricular predominance is not always associated with any particular type of tuberculosis. It is found more commonly in young than in old patients, and twice as frequently in men as in women.

3. Left ventricular predominance is not always associated with any particular type of tuberculosis. It is found more commonly in older patients, and is twice as frequent in women as in men.

4. Left ventricular predominance occurs more frequently with the increasing age of the patient.

5. In contrast to the necropsy findings reported in the literature, right ventricular predominance is not found more frequently in association with fibroid phthisis, or with pleural adhesions, than with other types of pulmonary tuberculosis.

FREQUENT CAUSES AND THE TREATMENT OF SEASONAL HAY-FEVER *

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BOSTON

Although John Bostock,[1] in 1819, first described the symptom complex of hay-fever, it was not until 1873 that Blackley [2] determined the real cause of the symptoms, namely, the pollen of plants. Curtis,[3] in 1900, was the first to attempt to produce active immunity or to treat the condition; he used extracts of the whole plant. Since Dunbar,[4] in 1905, was the first to employ extracts of the plant pollen, the modern treatment of hay-fever was really begun by him. During the past ten years reports on the treatment of hay-fever have been too numerous to justify reference to all of them in this paper, but the work of Noon, Freeman, Koessler, Cooke, Scheppegrell, Goodale, Selfridge and possibly of others justify the mention of their names since it is these who have done most toward establishing the treatment of seasonal hay-fever.

Notwithstanding the number of papers on the subject, there is a paucity of specificity as regards the pollens that actually cause hay-fever, and, likewise, the treatment of the condition has been stated too often in a general way. As a result, there would seem to be as many different pollens actually causing hay-fever and as many different ways of treating hay-fever as there have been investigators. A natural result was that commercial houses have put on the market pollen preparations consisting of mixtures of the various pollens that prevailed at definite seasons, and these mixtures were used by the medical profession all over the country. In other words, neither the physician nor the commercial house have been concerned as to whether any particular pollen was indigenous and caused hay-fever in one locality to the exclusion of other pollens in other localities, and the physician would not or could not determine by tests which of the prevailing pollens was the actual cause of symptoms; the pollen mixtures were used hit or miss. From the practical standpoint, the results from such treatment could not be as satisfactory as would be the case if the

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* From the medical clinic of the Peter Bent Brigham Hospital.

1. Bostock, J.: Case of Periodical Affection of the Eyes and Chest, Med. Chir. Tr., Lond. **10**:161, 1819.

2. Blackley, C. H.: Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay-Fever or Hay Asthma), London **7**:202, 1873.

3. Curtis, H. H.: The Immunizing Cure of Hay Fever, Med. News **77**:16 (July 7) 1900.

4. Dunbar, W. P.: Berl. klin. Wchnschr. **17**:797, 877, 915, 942, 1237, 1905; Deutsch. med. Wchnschr. **32**:578, 1911.

patient were treated by the pollens to which he was actually exposed and to which he was most sensitive. Therefore, the excuse for publishing the present paper in considerable detail is to help clarify the present status of the treatment of seasonal hay-fever as regards patients living in the New England States, and it is hoped that other investigators in the same and in other localities will be stimulated to detail their investigations. It is only by such detailed reports that it will be possible to learn the prevailing causative pollens in various localities and the best method of treatment.

After a description of the methods used by me in testing and treating hay-fever patients, this paper will consist of a series of tables. Table 1 presents those patients who were treated with ragweed pollen only one year; Table 2, patients treated with grass pollen only one year; Table 3, patients who had insufficient treatment with ragweed and with grass pollen; Table 4, patients treated two years in succession with ragweed pollen; Table 5, patients treated two years in succession with grass pollen; Table 6, patients treated three successive years with ragweed pollen; Table 7, those treated three successive years with grass pollen, and Table 8, those treated four successive years with ragweed pollen. In all of these tables the patients were treated preseasonally, thereby attempting to prevent symptoms. Table 9 presents patients who were treated during the season with grass pollen; Table 10, those treated during the season with ragweed pollen, and Table 11, patients treated during the season with bacterial vaccines. In these tables the patients were treated during the season, thereby attempting to relieve symptoms. Table 12 presents patients treated both preceding and during the season. The pollens of trees and pollens other than those already mentioned will be discussed as possible causes of hay-fever. Finally, other parts of plants, animal emanations, foods, bacteria and olfactory irritants will be discussed as causes of seasonal hay-fever.

The cutaneous or skin test, which has proven satisfactory to me,[5] was employed to determine the sensitivity of the patients to the various pollens. A number of small cuts, each about an eighth of an inch long, are made on the flexor surfaces of the forearm. These cuts are made with a sharp scalpel, but are not deep enough to draw blood, although they do penetrate the skin. On each cut is placed a pollen and to it is added a drop of tenth normal sodium hydroxid solution to dissolve the pollen protein and to permit of its rapid absorption. Instead of using the whole pollen, a concentrated solution of pollen protein or extract may be used without the addition of sodium hydroxid. At the end of half an hour the pollens are washed off and the reactions are

5. Walker, I. C., and Adkinson, J.: A Comparison Between the Cutaneous and the Intradermal Tests in the Sensitization of Asthmatic and Hay Fever Patients, J. M. Research **37**:287, 1917.

noted, always comparing the inoculated cuts with normal controls on which no pollen was placed. A positive reaction consists of a raised white elevation or urticarial wheal surrounding the cut. The smallest reaction that we consider positive must measure 0.5 cm. in diameter. All larger reactions are noted by a series of plus marks; any smaller reaction is called doubtful. The method of obtaining pollen from the flower has been outlined in Study 11.[6]

Having determined by these tests which pollens give a positive reaction, before a patient can be treated with the pollen it is necessary to know how sensitive that patient is to the pollen; therefore, different strengths of solutions of the pollen protein are tested in a similar manner. These solutions are made as follows: To 0.5 gm. of the dry pollen is added 44 c.c. of sterile physiologic sodium chlorid solution, and the mixture is shaken thoroughly at frequent intervals for twenty-four hours, after which enough absolute alcohol (6 c.c.) is added to the mixture to make the alcoholic content 12 per cent. Again, the mixture is thoroughly shaken at frequent intervals for twenty-four hours, after which it is centrifugalized at high speed and the supernatant fluid is pipetted off and saved. This supernatant fluid, therefore, consists of the pollen protein dissolved in a 12 per cent. alcoholic physiologic sodium chlorid solution and it represents, by weight, 1 part pollen to 100 parts solvent. This 1:100 solution is used as stock, and from it other dilutions, 1:500, 1:1,000, 1:5,000 and 1:10,000 are made, using a 12 per cent. alcoholic physiologic sodium chlorid solution as a diluent. These solutions are used not only for the skin tests but for treatment, and with the addition of a small crystal of thymol they keep for many months in a cool place.

Method of Treating Preseasonally with the Pollen Extracts Follows.—The first treatment consists of from 0.1 to 0.2 c.c. of that dilution next higher than the one which gave a positive skin test, or, in other words, the first dose is 0.1 c.c. or 0.2 c.c. of the strongest dilution which failed to give any skin reaction whatever, no matter how slight. With our pollen extracts the majority of patients whom we treated gave a more or less positive reaction with the 1:5,000 dilution, therefore, the first treatment consisted of 0.1 c.c. or 0.2 c.c. of the 1:10,000 dilution. Treatments were given subcutaneously once a week, and each week the amount of the extract was gradually increased, so that as the treatment progressed, stronger and stronger dilutions were used, until one or more doses of the 1:100 dilution were given. As an example, I will give what I have found by experimentation to be the best outline of treatment for a patient who gives a more or less positive skin test with a 1:5,000 dilution of pollen extract; 1:10,000, give 0.15 c.c.; 1:5,000,

6. Walker, I. C.: Studies on the Sensitization of Patients with Bronchial Asthma to the Various Pollens, J. M. Research **36**:237, 1917.

give 0.15 c.c., 0.25 c.c., 0.35 c.c., 0.45 c.c.; 1:1,000, give 0.15 c.c., 0.25 c.c.; 1:500, give 0.15 c.c., 025 c.c., 0.35 c.c., 0.45 c.c.; 1:100, give 0.15 c.c., 0.2 c.c., 0.25 c.c. Each dose was given preferably at weekly intervals and never oftener than once every five days.

This schedule of treatment calls for fourteen inoculations, however, for some reason or other, modifications frequently have to be used. An occasional patient is so sensitive to the pollen that a 1:10,000 dilution gives a slight reaction, thus necessitating an initial dose of 0.15 c.c. of 1:20,000 followed by possibly two doses of 1:10,000. Often it happens that a patient has considerable local or general reaction following some one treatment in the schedule, thus necessitating the repetition of that particular dose before the next increase may be given. More often the patient presents himself for treatment too late to complete the scheduled series of treatments before the onset of pollination so that for preseasonal treatment alone, some of the final treatments in the schedule must be omitted. This schedule is often modified purposely with certain individual cases. For instance, in some cases the second treatment with the 1:1,000 dilution, namely, 0.25 c.c., is omitted, and in some cases instead of giving 0.15 c.c. of the 1:100 dilution, when this happens to be the final treatment that the patient is to receive because of onset of pollination, a fifth treatment with the 1:500 dilution, namely, 0.55 c.c., is often substituted, and even a sixth treatment with the 1:500 dilution, namely, 0.65 c.c., is sometimes given. These larger doses of 1:500 approximate the amount of protein in 0.15 and 0.2 c.c. of the 1:100 dilution, therefore, the fifth and sixth treatment with the 1:500 dilution, as outlined, is practically the equivalent of giving 0.15 c.c. and 0.2 c.c. of the 1:100 dilution. Since by far the great majority of patients are treated from three to five times with the 1:500 dilution, and since this number of treatments has given fairly satisfactory results, I consider this number of treatments, which consists usually of a total of ten, as worth giving, although a continuance of the schedule beyond three doses of the 1:500 dilution is most desirable, and giving less than three treatments with the 1:500 dilution is undesirable. Tables 1 and 2 will illustrate the results obtained from giving three or more treatments with the 1:500 dilution, and Table 3 will illustrate the results obtained from giving less than three treatments with the 1:500 dilution.

Since in the New England States the majority of patients have the first hay-fever symptoms between Aug. 10 and 20, during which time the compositae, chiefly ragweed, begin to pollinate, in order to complete the above schedule just previous to the onset of symptoms and pollination, patients must begin treatment between the last week in April and the first two weeks in May. Beginning treatment the first week in June will permit of giving from three to five treatments with the 1:500

dilution. Likewise, since the early type of hay-fever, or so-called rose cold, which is usually caused by the grasses, begins the last few days of May or the first of June, treatment for this type of hay-fever should begin about the first of March, and the starting of treatment as late as the first of April will not permit of more than three or four treatments with the 1 : 500 dilution, according to the schedule outlined. Naturally, in localities outside of New England, these seasons would differ, and the beginning of treatment consequently would vary, also the causative pollen must differ.

Before Table 1 may be discussed, attention should be called to the following facts: In the New England States ragweed (*ambrosia artemisifolia,* or dwarf ragweed) is not the only plant that pollinates during August and September, nor is it the only pollen to which individuals are exposed or with which patients were tested. Most of the compositae, such as golden rod, sunflower, golden glow and aster, pollinate during August and September; daisy pollinates during June and July, and dandelion in the early spring; giant ragweed is rarely encountered in the New England States. In order to simplify the table, and because in my experience pollens other than ragweed rarely, if ever, are the chief cause of symptoms during the late hay-fever season, only ragweed is mentioned in the table although tests were made with the other pollens. During the years 1917, 1918 and 1919 all of the patients in Table 1 were tested with golden rod and daisy, and the majority were tested with golden glow and sunflower. During 1920, many of the patients were tested with these pollens. One hundred and twenty patients in Table 1 were tested with the pollens of daisy and golden rod, and 100 were also tested with the pollen of sunflower and golden glow. Fifty per cent. of those tested with golden glow and with sunflower gave a positive reaction with the whole pollen, but none of these gave a reaction with a 1 : 100 dilution of the pollen; the other 50 per cent. failed to react with the whole pollen. Therefore, it may safely be stated that the pollens of golden glow and sunflower are not primarily causes of hay-fever in New England. Of those tested with daisy pollen, 65.5 per cent. failed to react to a 1 : 100 dilution of daisy pollen; 21 per cent. did react to the whole pollen but not to a 1 : 500 dilution; 10 per cent. reacted more or less positively to a 1 : 500 dilution of the pollen, and only 3.5 per cent. reacted to as high a dilution as 1 : 1,000. Therefore, in comparison with ragweed, in only 3.5 per cent. could one consider that daisy might be a cause of hay-fever as judged by tests, but it should be borne in mind that daisy pollinates during June and July and has finished pollination before ragweed begins, therefore daisy cannot complicate the causes of August and September hay-fever. Of the 120 patients in Table 1 who were tested with golden rod pollen, 78.5 per cent. failed to react with a 1 : 100 dilution of the pollen; 10 per cent.

TABLE 1.—Preseasonal Tests and Treatment with Ragweed Pollen

Patient	Age of Onset	Duration	Tests Before Treatment	Number Treatments With Final Dilution	Tests at End of Treatment	Result of Treatment*	Patient	Age of Onset	Duration	Tests Before Treatment	Number Treatments With Final Dilution	Tests at End of Treatment	Result of Treatment
			Season 1917							Season 1920—Continued			
1	42	25	1-1,000±	1-100:4	.....	Good	97	9	8	1-10,000±	1-500:4	.....	Fair
2	8	7	1-5,000±	1-100:2	1-100+	Good	98	37	3	1-10,000±	1-500:5	1-500±	75%
3	44	30	1-1,000+	1-100:2	1-100+	Good	99	9	8	1-10,000±	1-100:2	.....	75%
4	18	10	1-5,000±	1-500:5	.....	Good	100	..	1	1-5,000±	1-500:6	.....	75%
5	17	21	1-5,000±	1-100:2	1-500±	Good	101	2	12	1-5,000±	1-500:5	.....	75%
6	26	4	1-5,000±	1-500:4	1-500+	Good	102	29	6	1-5,000+	1-500:4	.....	Fair
7	24	16	1-5,000±	1-100:3	1-500+	75%	103	15	30	1-10,000±	1-500:3	.....	50%
8	43	5	1-5,000±	1-500:3	.....	50%	104	30	15	1-10,000±	1-500:3	.....	50%
9	30	8	1-5,000+	1-500:6	.....	Good	105	23	1	1-1,000±	1-500:6	.....	75%
10	43	3	1-10,000+	1-500:4	.....	Good	106	29	40	1-5,000±	1-500:6	.....	50%
11	10	23	1-5,000±	1-100:4	.....	Good	107	..	8	1-5,000+	1-100:3	.....	75%
12	1	11	1-1,000±	1-500:3	.....	50%	108	24	1	1-5,000±	1-500:4	.....	None
							109	39	10	1-5,000±	1-500:5	.....	50%
			Season 1918				110	1	9	1-5,000+	1-500:5	.....	Fair
13	21	12	1-10,000±	1-500:4	.....	50%	111	12	9	1-10,000±	1-500:5	.....	50%
14	8	5	1-1,000±	1-100:2	.....	None	112	30	5	1-10,000±	1-500:5	.....	50%
15	..	..	1-1,000±	1-500:5	.....	None	113	8	27	1-5,000±	1-500:5	.....	75%
16	..	6	1-10,000±	1-500:4	.....	Good	114	3	2	1-5,000±	1-500:5	.....	Fair
17	52	3	1-5,000±	1-100:3	.....	Fair	115	30	5	1-5,000±	1-500:5	.....	50%
18	22	15	1-5,000±	1-500:4	.....	75%	116	41	2	1-5,000±	1-500:5	.....	75%
19	22	18	1-5,000±	1-500:5	.....	Good	117	2	17	1-10,000±	1-100:3	.....	Fair
21	24	30	1-10,000+	1-500:5	.....	None	118	8	23	1-10,000±	1-500:6	.....	Fair
20	38	20	1-5,000±	1-100:1	.....	50%	119	Infant	23	1-10,000±	1-500:4	.....	75%
22	25	4	1-5,000+	1-100:2	.....	Good	120	Infant	21	1-5,000±	1-500:5	.....	50%
23	24	4	1-5,000±	1-500:6	.....	75%	121	24	12	1-5,000±	1-500:5	.....	Good
24	33	25	1-10,000±	1-500:5	.....	None	122	30	8	1-5,000+	1-500:5	.....	Fair
25	26	20	1-1,000±	1-100:1	.....	Fair	123	12	5	1-10,000±	1-500:5	.....	75%
26	1	35	1-5,000±	1-500:3	.....	75%	124	Infant	33	1-20,000±	1-500:4	.....	50%
27	28	14	1-1,000±	1-500:4	.....	Good	125	10	5	1-10,000±	1-500:3	.....	75%
28	28	26	1-5,000±	1-500:5	.....	Good	126	35	7	1-5,000±	1-500:4	.....	75%
29	24	37	1-1,000±	1-500:4	.....	75%	127	2	47	1-5,000±	1-500:5	.....	Fair
30	39	17	1-5,000±	1-500:3	.....	Fair	128	14	10	1-5,000±	1-500:5	.....	Fair
31	27	4	1-1,000+	1-500:6	.....	Good	129	17	2	1-5,000±	1-500:4	.....	50%
32	7	10	1-5,000±	1-500:4	.....	75%	130	33	3	1-5,000±	1-500:3	.....	Fair
33	27	25	1-5,000+	1-500:4	.....	None	131	20	10	1-1,000±	1-500:5	.....	75%
34	18	22	1-5,000±	1-500:6	.....	50%	132	29	10	1-1,000+	1-500:5	.....	50%
35	19	15	1-5,000±	1-500:3	.....	50%	133	19	15	1-5,000+	1-500:5	.....	50%
35a	27	10	1-1,000±	1-500:4	.....	Fair	134	16	6	1-5,000±	1-500:3	.....	None
36	18	20	1-5,000±	1-500:4	.....	Good	135	27	12	1-10,000±	1-500:5	1-100	50%
36a	30	5	1-1,000±	1-500:4	.....	Good	136	49	5	1-20,000±	1-500:4	.....	75%
37	32	13	1-10,000±	1-500:4	.....	75%	137	34	1	1-20,000±	1-500:3	.....	50%
38	13	37	1-1,000±	1-100:3	.....	75%	138	4	6	1-5,000±	1-500:4	.....	Fair
39	4	10	1-5,000±	1-500:3	.....	Good	139	26	8	1-5,000±	1-500:4	.....	75%
40	19	4	1-5,000±	1-500:3	.....	50%	140	33	2	1-5,000±	1-500:3	.....	75%
41	18	19	1-5,000±	1-500:5	.....	75%	141	15	6	1-5,000+	1-500:5	.....	50%

			Season 1919				142	8	2	1-5,000±	1-500:4	.....	75%
42	24	15	1-10,000+	1-100:5	1-100+	75%	143	5	35	1-5,000±	1-500:5	.....	75%
43	39	45	1-10,000+	1-500:3	1-500±	Good	144	25	6	1-5,000+	1-500:5	.....	None
44	3	8	1-10,000+	1-100:2	1-100+	Good	145	32	10	1-10,000±	1-500:5	.....	Fair
45	32	8	1-10,000+	1-100:4	1-100+	50%	146	20	6	1-1,000+	1-500:4	.....	Fair
46	20	13	1-10,000±	1-100:5	1-500±	Good	147	10	20	1-5,000+	1-500:4	.....	75%
47	1	38	1-5,000+	1-500:4	.....	Fair	148	35	5	1-5,000+	1-500:5	.....	Fair
48	1	20	1-10,000+	1-100:2	1:500+	50%	149	22	8	1-10,000±	1-500:4	.....	75%
49	50	3	1-10,000±	1-500:5	.....	Good	150	33	4	1-5,000±	1-500:5	.....	50%
50	8	9	1-10,000+	1-100:2	1-100+	Good	151	16	4	1-5,000+	1-500:3	.....	75%
51	29	31	1-10,000+	1-100:3	1-100+	Good	152	24	2	1-5,000±	1-500:4	.....	50%
52	37	11	1-5,000±	1-500:5	1-100+	75%	153	9	45	1-10,000±	1-500:5	.....	Good
53	7	24	1-20,000+	1-100:3	1-100+	Good	154	20	2	1-5,000+	1-500:4	.....	75%
54	30	9	1-20,000+	1-100:1	1-1,000+	None	155	24	6	1-5,000+	1-500:5	.....	50%
55	37	4	1-10,000+	1-100:4	1-100+	None	156	21	20	1-5,000±	1-500:5	.....	75%
56	16	7	1-10,000±	1-500:4	.....	Fair	157	30	25	1-5,000±	1-500:5	.....	Fair
57	19	12	1-5,000+	1-100:4	1-100±	50%	158	4	3	1-500+	1-500:6	.....	50%
58	26	6	1-1,000±	1-500:5	1-100.0	Good	159	10	20	1-10,000±	1-500:4	.....	50%
59	17	19	1-5,000±	1-500:3	1-500+	50%	160	18	4	1-5,000±	1-100:1	.....	75%
60	2	17	1-5,000±	1-100:4	1-500±	75%	161	17	3	1-10,000±	1-500:4	.....	75%
61	28	16	1-5,000+	1-100:4	1:500+	Good	162	29	5	1-10,000±	1-500:4	.....	Fair
62	27	22	1-10,000±	1-500:5	.....	75%	163	36	2	1-20,000±	1-500:5	1-1,000±	Fair
63	22	30	1-10,000+	1-500:5	.....	75%	164	7	5	1-1,000+	1-500:5	.....	75%
64	10	3	1-500±	1-100:2	1-100.0	Good	165	19	1	1-500±	1-500:4	.....	75%
65	6	10	1-500+	1-100:4	.....	Good	166	..	25	1-20,000±	1-500:5	.....	75%
66	45	5	1-10,000±	1-100:3	1-100+	Good	167	30	5	1-5,000±	1-500:5	.....	75%
67	4	10	1-10,000±	1-100:2	1-500+	Good	168	5	4	1-5,000±	1-100:1	Pol. 0	50%
68	32	3	1-1,000±	1-500:4	.....	Good	169	15	3	1-10,000+	1-100:2	.....	75%
69	38	7	1-20,000+	1-100:2	1-1,000+	None	170	27	1	1-1,000+	1-500:3	.....	50%
70	22	6	1-1,000±	1-100:4	1-100.0	Good	171	19	8	1-10,000+	1-500:3	.....	50%
71	30	4	1-10,000±	1-500:2	.....	Fair	172	10	54	1-10,000+	1-100:1	.....	Good
72	27	7	1-10,000±	1-100:4	1-1,000±	None	173	14	10	1-10,000+	1-500:4	.....	75%
73	16	45	1-5,000±	1-500:4	.....	Good	174	26	2	1-10,000±	1-100:2	.....	75%
74	8	26	1-10,000+	1-500:5	1-500+	75%	175	19	2	1-5,000±	1-500:5	.....	Good
75	49	20	1-5,000±	1-100:4	1-100+	Good	176	18	7	1-5,000±	1-500:5	.....	Fair
76	39	16	1-500+	1-100:1	.....	Good	177	8	5	1-10,000±	1-500:4	1-1,000±	75%
77	36	37	1-10,000±	1-100:3	1-1,000±	Good	178	13	2	1-1,000±	1-100:2	1-5,000±	50%
78	17	3	1-10,000±	1-500:4	1-500±	Good	179	19	5	1-5,000+	1-100:3	.....	75%
79	25	10	1-10,000±	1-500:4	.....	50%	180	8	20	1-1,000+	1-100:3	1-100+	Fair
80	34	12	1-5,000+	1-100:3	1-100.0	Fair	181	3	9	1-10,000±	1-500:3	.....	50%
81	1	3	1-5,000+	1-500:5	.....	Good	182	26	10	1-5,000±	1-100:1	1-500±	75%
82	36	4	1-5,000±	1-100:2	1-500±	Fair	183	30	7	1-10,000±	1-100:2	1-500±	75%
83	22	18	1-5,000±	1-500:5	1-5,000±	None	184	10	8	1-40,000±	1-500:4	1-1,000+	50%
84	16	4	1-10,000±	1-100:1	1-100.0	Fair	185	28	10	1-10,000±	1-500:5	.....	50%
85	38	6	1-10,000±	1-100:1	1-100±	Fair	186	35	15	1-10,000±	1-500:5	1-500±	75%
							187	11	28	1-10,000±	1-500:4	.....	50%
			Season 1920				188	1	28	1-5,000+	1-100:4	1-100+	Good
86	14	7	1-5,000±	1-500:5	.....	Fair	189	16	6	1-20,000+	1-500:4	.....	50%
87	20	6	1-10,000+	1-500:5	.....	50%	190	20	10	1-1,000+	1-100:2	.....	Fair
88	44	8	1-10,000+	1-500:4	1-1,000±	50%	191	6	13	1-10,000±	1-500:5	.....	75%
89	18	10	1-20,000±	1-500:5	.....	50%	192	30	10	1-5,000±	1-500:5	.....	75%
90	15	2	1-5,000±	1-500:5	.....	75%	193	13	4	1-5,000±	1-500:5	.....	50%
91	28	20	1-10,000±	1-100:2	.....	Good	194	25	5	1-5,000+	1-500:6	.....	Fair
92	10	20	1-5,000±	1-500:4	1-100±	75%	195	4	5	1-5,000±	1-100:3	.....	50%
93	8	2	1-500+	1-100:4	.....	75%	196	..	5	1-5,000±	1-500:5	.....	Fair
94	33	12	1-5,000+	1-500:5	.....	Fair	197	8	14	1-10,000±	1-500:6	.....	50%
95	35	35	1-20,000+	1-500:5	1-500+	75%	198	27	20	1-10,000+	1-500:6	.....	75%
96	12	5	1-10,000±	1-500:4	.....	75%	199	15	25	1-10,000±	1-500:6	.....	75%
							200	28	20	1-5,000±	1-500:5	.....	Fair

* Fair in result column means practically free from symptoms, good means entirely free

did not react to a 1 : 500 dilution of the pollen; 8.25 per cent. did react more or less to a 1 : 500 dilution, and 3.25 per cent. reacted to a 1 : 1,000 dilution but no higher. Therefore, in comparison with ragweed, in only 3.25 per cent. of the cases in Table 1 could golden rod pollen be assumed as a possible cause of hay-fever. From the investigations of Scheppegrell [7] and others we know that the pollens of golden rod, sunflower, golden glow, daisy and aster are not carried by the wind, and that their pollens are heavy and shed very sparingly, so that for these reasons patients are not exposed to these pollens unless the flowers are kept in the house or unless sensitive patients smell of the flowers; naturally, the patient can refrain from such intimate contact and need not be treated for these.

Since the construction of Table 1 may not be entirely clear, the case of the second patient will be discussed in detail as an example of all of the remaining cases presented in this and similar tables. Patient 2 began to have hay-fever at the age of 8; he had had it for seven years; previous to treatment his skin test with ragweed pollen was slightly positive with a 1 : 5,000 dilution, therefore, treatment was begun with 0.15 c.c. of 1 : 10,000 dilution. The schedule of treatments was carried out until he was given two treatments with the 1 : 100 dilution; at the end of treatment his skin test was positive with the 1 : 100 dilution, but it should be assumed that the test was negative with weaker dilutions, namely, 1 : 500, etc.; the result was that the patient was free from hay-fever during the August and September season in 1917. Other symbols that may need explanation are the following: In the result column good means entirely free from symptoms, fair means practically free, that is, not entirely free from symptoms but much better than 75 per cent.; 75 per cent. and 50 per cent. mean that amount of freedom or benefit; none means no benefit or no relief; however, some of these patients did claim to be 25 per cent. relieved, but I do not wish to tabulate so little benefit.

The results of treatment from the symptomatic standpoint in the 202 patients presented in Table 1 were as follows: 45 patients, or 22 + per cent., had no symptoms; 36 patients, or 17 + per cent., were practically free from symptoms; 61 patients, or 30 + per cent., were benefitted at least 75 per cent.; 47 patients, or 23 + per cent., were benefited only 50 per cent., and 13 patients, or 6.5 per cent., were not benefited at all. Correlation of symptomatic benefit with the amount of treatment brings out the following facts: Of the forty-five patients who were entirely free from symptoms, twenty-three were given one or more treatments with the 1 : 100 dilution and twenty others were given four or more treatments with the 1 : 500 dilution. Of the thirty-six patients who

7. Scheppegrell, W.: Hay-Fever and Hay-Fever Pollens, Arch. Int. Med. **19**:959 (July) 1917.

were practically free from symptoms, one-fourth received the 1 : 100 dilution from one to three times, practically one-half of the series were given the 1 : 500 dilution five or six times, and nearly one-fourth were treated four times with this dilution. Of the sixty-one patients who were 75 per cent. improved, practically one-fifth were treated from one to five times with the 1 : 100 dilution, nearly one-half were treated five or six times with the 1 : 500 dilution, a few more than one-third were treated four times with the 1 : 500 dilution. Of the forty-seven patients who were 50 per cent. relieved, only seven, or approximately one seventh, were treated with the 1 : 100 dilution, approximately three eights were given the 1 : 500 dilution five or six times, about one fifth were given four treatments with the 1 : 500 dilution, and nearly one fourth were given only three treatments with the 1 : 500 dilution. The thirteen patients who were not benefited will be discussed in detail later. Therefore, it is very evident that one or more treatments with the 1 : 100 dilution yielded the best results, and that five or more treatments with the 1 : 100 dilution yielded the best results, and that five treatments with the 1 : 500 dilution gave considerable better results than four treatments with this dilution, although four treatments with the 1 : 500 dilution are well worth giving; as the number of patients who were treated three times with the 1 : 500 dilution increased, the amount of benefit gradually decreased, until nearly one quarter of the 50 per cent. benefited fell into this group; in other words, only three treatments with the 1 : 500 dilution give poor results in comparison to giving four or better still five treatments with this dilution. When one stops to consider that the fifth or sixth treatment with the 1 : 500 dilution is equivalent in amount of protein to at least one treatment with the 1 : 100 dilution, it is very evident that five or six treatments with the 1 : 500 dilution, or one treatment with the 1 : 100 dilution, is the ideal treatment.

Although little information is obtained by analyzing the table in regard to why some patients were more benefited than others, and why some were not benefited at all, after all it does seem worth doing.

Concerning the thirteen patients who were not improved, none gave positive skin tests with the pollens of daisy, golden rod, golden glow or sunflower. The treatment of Patient 144 was given at irregular intervals; Patient 134 lost three weeks during treatment so that he could be given only three doses of the 1 : 500 dilution; Patient 108 was given only four doses of the 1 : 500 dilution; even though many other patients were greatly benefited by similar treatment, it may be fair to assume that the negative result with these three particular cases was due to insufficient treatment. Patient 83 gave as positive a skin test at the end of treatment as he did before treatment, and the last treatment produced an anaphylactic shock manifested by urticaria.

Patients 72, 69 and 54 gave positive skin tests with a 1 : 1,000 dilution at the end of treatment, in spite of the fact that they all had received the 1 : 100 dilution one or more times. It may be safely stated that in the case of these four patients treatment did not desensitize the skin, and it is likewise probably true that, for some unknown reason, the patient's mucous membranes were not desensitized or that there was lack of union between the patients' antibodies and the treatment antigen. Patient 55 received four doses of the 1 : 100 dilution and at the end of treatment no dilution stronger than the 1 : 100 gave a positive reaction, and Patient 14 was treated with the 1 : 100 dilution two times so that these two patients ought to have had sufficient pollen treatment. Patients 33, 24, 21 and 15 all received the 1 : 500 dilution five times so that they also did not fall short of the average amount of treatment. The varying ages of onset and years of duration of symptoms, and the approximately equal distribution between the two sexes and between the three different years, furnish no clues toward the cause of failure from treatment. It would seem that we must blame the individuality or idiosyncrasy of these particular patients for the time being, and, therefore, it should be admitted that with our present knowledge there are a few hay-fever victims who are not benefited by preseasonal pollen therapy.

Of the forty-seven patients who were only 50 per cent. improved, three showed evidence of lack of desensitization, as was noted in the previous paragraph, in that one case following four treatments with the 1 : 500 dilution and another following six similar treatments gave positive skin tests with a 1 : 1,000 dilution of the pollen protein; the third gave a positive skin test with the 1 : 5,000 dilution following two doses of 1 : 100, and it is interesting that this patient was not shocked. It is difficult to explain why fifteen patients who were treated five times with the 1 : 500 dilution, and three patients who were similarly treated six times should not receive more than 50 per cent. relief when so many more experienced greater benefit from the same treatment. It is still more difficult to understand why the six patients who were treated from one to four times with the 1 : 100 dilution of pollen protein should be only 50 per cent. improved, especially since at the end of treatment one patient gave negative tests with the whole pollen protein and two others gave positive reactions with no stronger than the 1 : 100 dilution.

Attention should be called to the decreased sensitivity of the patient as evidenced by the skin test following a satisfactory series of treatments. Fifty-one patients were tested at the end of treatment. One third of these gave a more or less positive skin test with the 1 : 100 dilution but did not react to a more dilute solution of the pollen protein; the same number gave a more or less positive skin test with the 1 : 500 dilution but failed to react to a more dilute pollen protein solution; one half of these were given treatments with the 1 : 100 dilution, and the

other half with the 1 : 500 dilution; a few were given only three doses of the 1 : 500 dilution; five failed to react at all with the 1 : 100 dilution, four were treated with the 1 : 100 dilution; one patient who was treated with the 1 : 100 dilution failed to react to the whole pollen; eight gave a more or less positive skin test with the 1 : 1,000 dilution, four having been treated with the 1 : 100 dilution without producing ill symptoms; two patients reacted with the 1 : 5,000 dilution of pollen protein—one, Patient 83, was shocked (urticaria) following the fifth treatment with a 1 : 500 dilution and was unimproved, whereas the other, Patient 178, had received two doses of the 1 : 100 dilution but was not shocked and was 50 per cent. improved. Therefore, in all but two cases, treatment decreased the sensitivity of the patient, as evidenced by the skin test; or to be more specific, in practically three-fifths of the cases the intensity of the skin test diminished 100 times and in practically the remaining two fifths it was decreased at least twenty times; the larger the number of treatments given, the greater was the decrease in the intensity of the skin test.

Pollens, other than ragweed, that might complicate the cause and treatment of hay-fever at this season of the year in New England have already been mentioned, and to a certain extent these have been eliminated. Since, however, a few paients listed in Table 1 did react rather strongly to other pollens, it may be advisable to mention them. Patients 4, 6, 23 and 29 gave more or less positive skin tests with a 1 : 1,000 dilution of daisy but the first two were free from symptoms and the other two were 75 per cent. benefited by six and four treatments, respectively, of a 1 : 500 dilution of ragweed pollen alone. Patient 26 reacted to a 1 : 1,000 dilution of corn pollen but was 75 per cent. improved by three doses of 1 : 500 dilution of ragweed pollen. Patients 19, 28 and 74 reacted more or less to a 1 : 1,000 dilution of golden rod pollen, but following five treatments with 1 : 500 ragweed pollen, Patients 19 and 28 were free from symptoms, and Patient 74 was 75 per cent. benefited. Therefore, for reasons already stated, it would seem that pollens other than ragweed played no part in the cause of hay-fever at this particular season.

The age at which hay-fever began, and the number of years that the patient has had hay-fever, seem to play no part in the cause or the treatment of this type of hay-fever. Neither does the sex of the patient have any bearing even on the frequency of the condition. The patients in Table 1 were equally divided between the two sexes. A number of the patients were treated at five day intervals rather than, as was usually the case, at seven day intervals. Although statistics would not reveal any information on this point, it is my impression that the seven day interval is preferable to the five day interval. The individuality of the

patient certainly plays a great part in the treatment and in the results of treatment of hay-fever; however, any definite information in regard to this point cannot be obtained.

The same season in different years varies greatly in regard to the abundance of pollen, the beginning and the end of pollination and the frequency of colds that may be mistaken for hay-fever and thereby complicating the results of treatment. For example, in 1918, ragweed began to pollinate about August 8; in 1918 and 1919, frosts sufficiently heavy to stop pollination occurred about the middle of September, and even during all of September the weather was cold and rainy, so that not only was pollination below normal but head colds were frequent and the influenza epidemic was present. The season of 1920 was very favorable for ragweed; no frosts severe enough to injure it occurred, and pollination continued from about August 13 until October 1, at which time the plant naturally completed pollination and went to seed. There was no epidemic of colds and very little rain. For these reasons the results of preseasonal or preventive treatment with ragweed pollen in 1920 are of great value and are a true test for the treatment. Before considering these results, however, it should be noted that the amount of treatment given in this particular year was, in general, less than that given in preceding years. On referring to Table 1, season of 1920, the following are seen to have been the results of ragweed treatment; of the 115 patients treated, 27 per cent. experienced little or no hay-fever; 40 per cent. were 75 per cent. relieved; about 66 per cent. were, therefore, either 75 per cent. relieved or more so, and less than 33 per cent. had as little as 50 per cent. relief, whereas only three patients, or 2.6 per cent., were not benefited by treatment.

Before Table 2 is discussed, attention should be called to the plants that pollinate during June and July, the early hay-fever or so-called rose cold season. In the New England States some of the compositae, the most important of which is daisy, pollinate at this time but for reasons already given daisy pollen rarely, if ever, is a cause of hay-fever. Such plants as the lilies, sorrel, buttercup and others pollinate at this time, but when tested no patient has been found to be sensitive to these, and if they ever cause hay-fever it is because of immediate nasal contact with the blossom. The rose which pollinates at this time is rarely a cause of hay-fever since it is not a wind pollinated plant. Since, however, rose is commonly suspected to be the cause of hay-fever or rose colds, and since the pollen of rose is occasionally the actual cause, skin tests with rose pollen frequently have to be done, if for no other reason than to satisfy the patient. Although in Table 2 only two patients (219 and 226) are represented as having been tested with rose pollen, thirty-three others of the fifty-two were tested with rose, and thirty-one failed to react more than doubtfully with the whole pollen of either

the red or the white rose, and the two who did give a positive skin test with the whole pollen failed to react at all with a 1 : 100 dilution of the pollen. The thirty-five patients who were tested with rose pollen were tested with it because they thought roses caused their hay-fever, and the other patients in Table 2 were not tested with it because they were sure that roses did not cause their hay-fever. Therefore, it would seem that in New England rosese were rarely the chief cause of hay-fever.

The cause of hay-fever during June and July in the New England States is practically limited to the pollens of the grass family. Lawn grass begins to pollinate early in May, as a rule, but since it is rare for hay-fever to begin early in May, lawn grass pollen is probably rarely, if ever, the chief cause of hay-fever. Since, however, lawn grass continues to pollinate throughout the summer even when it is repeatedly mowed closely, with those patients who are sensitive to the pollens of other grasses and are either not treated or are insufficiently treated with the particular grass pollen that is the chief cause of hay-fever, exposure to lawn grass pollen may be a complicating cause or may aggravate the symptoms of hay-fever. Orchard grass pollinates during July, but this type of grass grows in more or less secluded places, and it is not commonly encountered. The same thirty-five patients who were tested with rose pollen were also tested with orchard grass pollen. Thirty of them failed to give positive skin tests with the whole pollen, and the five who gave a positive test with the whole pollen failed to react with a 1 : 100 dilution of the pollen extract; therefore, orchard grass rarely, if ever, is an actual cause of hay-fever. Since corn is a member of the grass family, and since the table variety pollinates during July, it must be considered among the possible causes of early hay-fever. Forty of the fifty-two patients presented in Table 2 were tested with sweet corn pollen; twenty-two failed to react at all, and eighteen gave a positive skin test with the whole pollen, although no tests with a 1 : 100 dilution of the pollen extract were positive. The large number of positive tests with the whole pollen was probably due, in part, at least, to the very large amount of protein present in corn pollen in comparison to the small amount of protein present in other pollens. Corn pollen is very heavy, it rapidly descends to the ground and is carried by air currents or wind only a few feet, therefore, intimate exposure would be required to produce symptoms; furthermore, only rarely would a person be unable to avoid it. Therefore, corn pollen must rarely, if ever, be considered a cause of hay-fever in the New England States where no large acreage exists in any locality as is the case in the West. This same statement is, likewise, true of wheat, oats, barley and rye.

The grasses, then, with which we are concerned in New England are June grass, timothy and redtop, the pollens of which are light and are carried by wind considerable distances.[7] June grass begins to pollinate

TABLE 2.—PRESEASONAL TESTS AND TREATMENTS WITH GRASS POLLENS

Patient	Age of Onset	Duration	Tests Before Treatment			Number of Treatments With Final Dilution			Tests at End of Treatment			Result of Treatment
			Timothy	Red Top	June Grass	Timothy	Red Top	June Grass	Timothy	Red Top	June Grass	
							Season 1917					
201	50	10	1-1,000±	1-1,000±	.....	1-100:2	.....	.....	.....	.....	.....	Good
202	14	8	1:10,000±	1-1,000±	.....	1-500:3	.....	.....	.....	.....	.....	Good
203	23	18	1-500±	1-1,000±	.....	.....	1-100:3	.....	.....	.....	.....	50%
204	12	40	1-5,000+	1-1,000±	.....	1-500:3	.....	.....	.....	.....	.....	Good
205	30	5	1-1,000+	1-1,000±	.....	1-100:1	.....	.....	.....	.....	.....	75%
206	10	9	1-5,000±	1-100+	.....	1-500:3	.....	.....	1-100.0	.....	.....	Good
207	27	10	1-1,000±	1-500±	.....	1-100:3	.....	.....	1:100.0	.....	.....	Good
208	6	5	1-1,000+	1-100±	.....	1-100:3	.....	.....	1-100±	.....	.....	Good
209	7	14	1-5,000±	1-5,000±	.....	1-100:3	.....	.....	.....	.....	.....	Good
							Season 1918					
210	25	7	1-10,000±	1-5,000±	.....	1-100:1	.....	.....	.....	.....	.....	Good
211	34	10	1-1,000±	1-5,000±	.....	1-100:1	1-100:1	.....	.....	.....	.....	Good
212	27	18	1-1,000±	1-1,000±	.....	1-100:2	1-100:2	.....	.....	.....	.....	Good
213	19	4	1-5,000+	1-1,000+	.....	1-100:1	.....	.....	.....	.....	.....	Good
214	32	13	1-500+	1-500+	.....	1-100:2	.....	.....	.....	.....	.....	Good
215	13	6	1-5,000±	1-500±	.....	1-100:3	.....	.....	.....	.....	.....	Good
216	5	11	1-1,000+	1-100.0	.....	1-100:4	.....	.....	.....	.....	.....	Fair
							Season 1919					Good
217	20	15	1-5,000±	1-1,000±	1-1,000±	1-100:2	.....	.....	1-100±	1-1,000±	1-1,000±	Good
218	33	12	1-1,000+	1-1,000+	1-1,000+	1-100:3	.....	.....	1-100±	1-500±	1-500±	Good
220	7	2	1-5,000±	1-1,000±	1-5,000±	1-100:3	.....	.....	1-100±	1-500+	1-500+	Good

221	20	8	1-1,000+	1-1,000+	1-1,000+	1-500:3	.....	.....	.....	.....	.....	50%
222	..	..	1-5,000±	1-1,000±	1-1,000±	1-500:4	.....	.....	.....	.....	.....	Good
223	1	37	1-5,000±	1-5,000±	1-5,000±	1-500:5	.....	.....	1-500±	1-500±	1-500±	Good
224	8	3	1-1,000±	1-1,000±	1-1,000+	.....	1-500:4	.....	.....	.....	.....	50%
225	12	5	1-1,000±	1-500+	1-1,000±	1-500:4	.....	.....	.....	.....	.....	Fair
							Season 1920					
227	9	2	1-5,000±	1-5,000±	1-5,000±	1-500:4	.....	.....	.....	.....	.....	75%
228	3	11	1-1,000±	1-1,000+	1-1,000+	1-500:3	.....	1-500:3	.....	.....	.....	75%
229	23	4	1-5,000±	1-5,000+	1-1,000+	1-500:6	.....	1-500:4	.....	.....	.....	50%
230	23	6	1-5,000±	1-5,000±	1-500+	1-500:4	.....	1-500:2	.....	.....	.....	75%
231	8	5	1-10,000+	1-10,000+	1-5,000+	1-500:4	.....	1-500:4	.....	.....	.....	50%
232	29	15	1-1,000+	1-1,000±	1-500±	1-500:5	.....	.....	.....	.....	.....	50%
233	11	3	1-10,000+	1-10,000+	1-10,000+	1-500:3	.....	1-1,000:3	.....	.....	.....	75%
234	23	25	1-1,000±	1-1,000±	1-5,000±	1-500:3	.....	1-500:2	.....	.....	.....	50%
235	21	30	1-10,000±	1-1,000+	1-5,000±	1-500:4	.....	1-500:1	.....	.....	.....	Fair
236	36	11	1-5,000+	1-1,000+	1-5,000+	1-500:3	.....	1-1,000:2	.....	.....	.....	50%
237	13	4	1-1,000+	1-1,000+	1-1,000+	1-500:4	.....	.....	.....	.....	.....	None
238	12	4	1-5,000±	1-5,000±	1-5,000+	1-500:4	.....	1-500:2	.....	.....	.....	50%
239	20	2	1-500+	1-5,000±	1-1,000+	1-500:4	.....	1-500:4	.....	.....	.....	Good
240	22	8	1-5,000±	1-5,000+	1-5,000+	1-100:1	.....	1-500:4	.....	.....	.....	75%
241	15	12	1-1,000+	1-5,000±	1-5,000±	1-100:1	.....	1-500:2	.....	.....	.....	None
242	7	5	1-500+	1-500±	1-100+	1-500:4	.....	1-500:4	.....	.....	.....	Fair
243	6	40	1-5,000+	1-5,000±	1-5,000±	1-500:2	.....	.....	.....	.....	.....	75%
244	30	22	1-5,000+	1-5,000+	1-5,000+	1-500:4	.....	1-500:4	.....	.....	.....	Fair
245	19	1	1-1,000±	1-500+	1-1,000±	1-500:5	.....	1-500:5	.....	.....	.....	75%
246	1	20	Negative	1-1,000±	Negative	.....	1-100:4	.....	.....	.....	.....	Fair
247	4	4	1-5,000+	1-1,000±	1-5,000+	1-500:5	.....	1-1,000:2	.....	.....	.....	Fair
248	..	4	1-5,000+	1-500±	1-1,000+	1-500:5	.....	.....	.....	.....	.....	None
249	21	20	1-5,000±	1-1,000+	1-5,000+	1-500:4	.....	.....	.....	.....	.....	75%
250	16	19	1-5,000+	1-1,000+	1-5,000+	1-500:5	.....	.....	.....	.....	.....	75%
251	..	..	1-500+	1-100.0	1-500±	1-500:5	.....	1-500:5	.....	.....	.....	Fair
252	14	9	1-500±	1-500+	1-500±	1-100:5	.....	.....	.....	.....	.....	Good
219	..	3	1-1,000±	1-1,000±	1-1,000± Rose 1-500+	.....	1-500:5	Rose 1-500:5	.....	.....	.....	Fair
226	26	38	Negative	Negative	Rose 1-500+	.....	Negative	Rose 1-500:3	.....	.....	.....	Good

some years as early as the middle of May; when the season is very late, it does not pollinate before the last day or two in May; pollination continues for about three weeks. Timothy and redtop begin to pollinate between the middle of June and the first of July, depending on the season, and pollination continues until the middle or last of July; usually, the season of pollination lasts about six weeks. Therefore, in order to complete the schedule of treatments mentioned earlier in this paper as being desirable, preseasonal treatment with June grass must begin the first of March at the latest, and with timothy and redtop it must begin the middle of March.

Analysis of Table 2 shows the results of preseasonal treatment for the early type of hay-fever. Of the fifty-two patients treated, twenty-one, or 40.4 per cent., were free from symptoms; nine, or 17.3 per cent., were practically free from symptoms; ten, or 19.2 per cent., were 75 per cent. relieved; nine, or 17.3 per cent., were 50 per cent. relieved, and three, or 5.8 per cent., were not benefited. Twenty-eight of the patients were treated with timothy grass pollen alone, three with redtop alone, one with rose alone, two with timothy and redtop together, one with redtop and rose together and seventeen with timothy and June grass pollens together. Although these facts are of interest, much valuable information is missed unless particular attention is given to each year, therefore, each year will be discussed separately.

During the season 1917, nine patients were treated. Only one patient (203) was treated with redtop pollen, because this patient was more sensitive to dilutions of redtop pollen extract than to timothy pollen extract; the remaining eight patients were treated with timothy pollen extract alone because all but two were more sensitive to timothy pollen extract than to redtop pollen extract and since these two were equally sensitive to both pollen extracts, timothy was selected for treatment because it was thought that timothy was more prevalent than redtop. Judging from the excellent results and the decreased sensitivity of the patients, there is every reason to believe that all patients had a sufficient number of treatments, that all but two, who were 50 and 75 per cent., respectively, relieved by treatment with redtop pollen extract, were treated by the proper pollen. As a matter of fact, the two patients who were only 50 per cent. and 75 per cent. relieved had most of their symptoms during June rather than in July which fact would make one suspicious that some pollen other than those tested was the cause of symptoms; tests were made with orchard grass, corn and rose, none of which reacted in a dilution of 1:100, but June grass, which also pollinates during June, was not tested. With the exception of these two cases, timothy pollen extract would seem to have protected against redtop exposure since five of the patients were very sensitive to redtop pollen extract.

During 1918, seven patients were treated, and all but one were free from symptoms and that one was practically free. All patients were treated one or more times with the 1 : 100 dilution and all but two were treated with timothy pollen extract alone; these two were treated with the extracts of timothy and redtop pollens together. Therefore, the same conclusions that were drawn from the 1917 series hold true for the 1918 series, namely, that all patients had a sufficient number of treatments, that treatment with timothy pollen extract protects against redtop exposure, that, as a rule, patients are more sensitive to timothy pollen than to any other pollen prevalent at that time, with the possible exception of June grass which was not tested, and that the reason why two patients were treated with redtop pollen in addition to timothy pollen was because one was more sensitive to redtop than to timothy and the other was equally sensitive to both.

During 1919, eight patients were treated with the result that five were free from symptoms, one other was practically free, and two were only 50 per cent. relieved. Of the two patients (221 and 224) who were only 50 per cent. benefited, one had only three treatments with timothy pollen extract 1 : 500 and the other was treated with redtop instead of timothy; both patients had more sympoms in June than in July. Therefore, as regards timothy and redtop the same conclusions that were true of 1917 and 1918 were equally true for 1919. In 1919, tests were made with June grass and on referring to the table, season 1919, it will be seen that the eight patients reacted as strongly to June grass pollen as to redtop; some reacted more strongly to it, and all but two were as sensitive to June grass as to timothy pollen extract. It is also noted that four patients, who were tested with the three grass pollens at the end of timothy pollen treatment, showed a much greater decrease in sensitiveness to timothy pollen than to redtop or to June grass pollen. Therefore, since there is evidence that timothy pollen treatment seems to protect against redtop pollen exposure, as has already been shown, and since the patients in 1917 and 1919 who were least benefited by treatment, either by timothy or redtop, had most of their symptoms during the usual time of June grass pollination rather than during the time that timothy and redtop pollinate, and since in 1919 it was shown that early hay-fever patients are very sensitive to June grass pollen extract, it was deemed best to treat suitable patients with June grass pollen during 1920.

During the 1920 season, only three of twenty-eight patients were to any extent less sensitive to June grass pollen extract than to timothy pollen extract, and three of the patients were more sensitive to June grass pollen than to timothy. Therefore, in seventeen patients treatment was given with June grass pollen extract together with timothy pollen extract. The results of this mixed treatment were: one patient

was free from symptoms, five were practically free, five were 75 per cent. relieved, five were 50 per cent. relieved, and one was not benefited; a very poor showing as compared to treatment with timothy pollen extract alone during the three previous years. It is also noted that only two patients who were treated with the mixture were given as many as one treatment with timothy, 1 : 100, which is desirable and which was the case in previous seasons when excellent results were obtained; treatment with a mixture of the two pollens did not and will not permit of sufficient treatment with either one, and in this instance it is evident that a part, at least, of the poor results, if the three former seasons are a guide, was due to insufficient treatment with timothy pollen. The absence of treatment with redtop pollen cannot explain the poor results, since in the three former seasons excellent results were obtained in the absence of redtop treatment.

Special attention is called to Patients 246, 219 and 226 because their cases are of considerable interest. Patient 246 was sensitive to redtop pollen alone and was practically free from symptoms following four treatments with the 1 : 100 dilution of redtop pollen extract. Not only was this patient free from symptoms while in New England, but he was also free while in Wyoming and was practically free while in California. Patient 219, who was practically equally sensitive to the pollens of the three grasses and to rose, was practically free from symptoms following treatment with equal parts of redtop and rose pollen extracts. Patient 226, who was sensitive to rose pollen only, was free from symptoms following treatment with rose pollen extract. Therefore, only two rose cases were encountered in the four seasons during which fifty grass cases were tested and treated.

My conclusions, based on a four year's experience with the treatment of June and July hay-fever, are: While the pollen of timothy grass is the chief cause of hay-fever, and sufficient treatment with it alone gives excellent results, it is necessary to test all patients with the pollens of redtop, June grass and rose since an occasional patient is more sensitive to one of these pollens than to timothy pollen, and, therefore, such a patient may need treatment with one of them rather than with timothy pollen. When the same patient, as is frequently the case, is equally sensitive to the dilutions of the pollen extracts of timothy, redtop and June grass, it is advisable to treat the patient with timothy pollen extract alone because there is sufficient evidence that treatment with timothy pollen will protect against redtop pollen exposure, provided one or more treatments are given with the 1 : 100 dilution of the pollen extract; timothy and redtop pollinate at the same time, and redtop is less prevalent than timothy. Sufficient treatment with timothy pollen extract seems to protect also against June grass pollen exposure, but since, as is often the case, June grass pollination is well

advanced or even sometimes completed before timothy pollination begins, the patients being treated with timothy have not had sufficient treatment with timothy pollen to protect them completely against June grass pollen, consequently some of these patients will have more or less symptoms from June grass exposure, as happened in 1917 with Patients 203 and 205; in 1919, with Patients 221 and 224, and in 1920 with Patients 232 and 249. In 1918, when June grass pollination was

TABLE 3.—INSUFFICIENT POLLEN TREATMENT

Patient	Age of Onset	Duration	Tests Before Treatment	Number of Treatments With Final Dilution	Result of Treatment
Ragweed					
253	22	13	1-10,000+	1-1,000:2	None
254	22	4	1-5,000±	1-1,000:3	50%
255	3	10	1-5,000±	1-1,000:3	75%
256	18	5	1-1,000±	1-1,000:3	50%
257	14	24	1-5,000±	1-1,000:2	50%
258	16	45	1-5,000±	1-1,000:2	50%
259	19	15	1-5,000±	1-1,000:2	25%
260	28	14	1-1,000+	1-1,000:2	75%
261	13	9	1-5,000±	1-1,000:3	50%
262	39	10	1-5,000+	1-1,000:3	None
263	31	2	1-1,000±	1-500:2	None
264	3	9	1-10,000+	1-5,000:4	None
265	6	12	1-10,000+	1-1,000:2	50%
266	16	7	1-10,000±	1-1,000:3	75%
267	44	10	1-10,000±	1-5,000:5	50%
289	16	45	1-10,000±	1-500:2	50%
268	27	12	1-10,000±	1-500:2	50%
269	44	6	1-5,000+	1-500:2	50%
271	14	9	1-5,000±	1-1,000:2	None
272	9	2	1-5,000±	1-5,000:5	50%
273	14	10	1-5,000+	1-500:2	None
274	29	3	1-10,000±	1-5,000:1	50%
275	3	49	1-10,000±	1-500:2	None
276	3	6	1-20,000±	1-5,000:3	50%
277	9	9	1-10,000±	1-500:2	50%
278	3	20	1-10,000±	1-5,000:4	50%
279	16	16	1-10,000±	1-500:1	None
280	5	19	1-10,000±	1-1,000:2	50%
281	18	3	1-10,000±	1-500:2	75%
282	35	12	1-10,000±	1-1,000:2	Fair
283	31	6	1-10,000±	1-500:2	75%
284	35	15	1-10,000±	1-500:2	50%
285	13	16	1-1,000+	1-500:2	75%
294	11	7	1-5,000±	1-500:2	50%
295	31	5	1-5,000±	1-500:2	None
296	20	17	1-5,000±	1-500:1	50%
297	22	25	1-5,000±	1-500:2	75%
298	11	7	1-5,000±	1-500:2	50%
299	37	18	1-5,000±	1-500:2	50%
270	41	7	1-5,000±	1-500:2	50%
Timothy					
286	30	4	1-5,000±	1-1,000:2	None
287	19	10	1-10,000±	1-5,000:3	None
288	30	5	1-5,000±	1-1,000:3	50%
290	14	6	1-5,000±	1-1,000:2	None
291	8	3	1-1,000±	1-500:2	50%
292	14	14	1-10,000±	1-500:2	None
293	22	5	1-10,000±	1-5,000:5	50%

late, timothy treatment was successful, and the few cases in Table 2 that were tested with the three grass pollens at the end of much timothy treatment alone, were considerably less sensitive to all of the grass pollens and all of the patients were free from symptoms. Unless treatment with June grass pollen is begun earlier than is customary with timothy pollen, patients will not be treated sufficiently with June

grass pollen. Therefore, treatment with both timothy pollen and June grass pollen extracts together will not only be insufficient to protect against early June grass pollination (Patients 229, 233, 234 and 238, all of whom had symptoms in late May and early June), but the combination of the two pollen extracts necessarily retards and diminishes the amount of treatment that might be given with timothy alone. Table 2 shows this to be the usual case. Therefore, I am opposed to preseasonal treatment with pollen mixtures, except on rare occasions, and in the case of June grass it is better to take a chance on a late season with timothy protection or even an early season with few symptoms than to treat with it in conjunction with timothy when timothy treatment is essential.

In Table 3 are presented patients who had insufficient pollen treatment, and by insufficient is meant that for some reason or other the complete schedule of treatments, as outlined early in this paper, could not be given. A few of the patients did receive the 1 : 500 dilution of the pollen extract two times, but for reasons already stated I consider this insufficient treatment.

In Table 3 are presented forty patients who were given insufficient treatment with ragweed pollen extract, and seven patients similarly treated with timothy pollen extract. The possibility of sensitization to pollens, that might be the cause of symptoms, other than ragweed and timothy will not be considered in the light of previous discussion. The results were as follows: Of the forty-seven patients in Table 3, none were free from symptoms, one was practically free, seven were 75 per cent. benefited, twenty-five were 50 per cent. benefited, one was 25 per cent. benefited and the remaining thirteen were not benefited. Therefore, although a few patients may be from 50 to 75 per cent. benefited by as small a number as two treatments of the 1 : 500 dilution, these results are offset by the number of failures resultant from similar treatment, and this is still more evident when a smaller amount of treatment than two doses of the 1 : 500 dilution is given. The results shown in Table 3 verify what has already been proven in Tables 1 and 2, namely, that giving less than three preseasonal treatments with the 1 : 500 dilution of pollen extract is undesirable.

In Table 4 are presented seventy-three patients who were treated with ragweed pollen extract two years in succession. Six patients were treated in the two seasons 1917 and 1918; fifteen, in 1918 and 1919, and fifty-two in 1919 and 1920.

Analysis of Table 4 shows that for the first year of treatment, of the seventy-three patients, twenty-eight, or 38 + per cent., were free from symptoms; sixteen, or 22 per cent., were practically free; fourteen, or 19 + per cent., were 75 per cent. relieved; twelve, or 16.4 per cent., were 50 per cent. benefited, and three, or 4 + per cent., were

TABLE 4.—Preseasonal Tests and Treatment with Ragweed Pollen Two Successive Years

Patient	Age of Onset	Duration	Season 1917				Season 1918			
			Tests Before Treatment	No. Treatments With Final Dilution	Tests at End of Treatment	Result of Treatment	Tests Before Treatment	No. Treatments With Final Dilution	Tests at End of Treatment	Result of Treatment
300	16	10	1-1,000±	1-100:2	.....	Good	1-1,000±	1-100:2	.....	Good
301	..	10	1-1,000±	1-100:3	.....	Good	1-5,000±	1-100:1	1-500±	Good
302	45	3	1-5,000±	1-100:1	.....	Good	1-500±	1-500:5	.....	Good
303	39	10	1-5,000+	1-500:4	.....	Good	1-5,000+	1-100:2	.....	Good
304	20	10	1-5,000±	1-100:3	.....	Good	1-5,000±	1-500:5	.....	75%
305	32	6	1-5,000+	1-500:4	.....	75%	1-1,000+	1-100:1	.....	Good
			Season 1918				Season 1919			
306	24	25	1-5,000±	1-500:5	.....	Good	1-5,000±	1-500:5	.....	75%
307	14	15	1-5,000±	1-100:2	.....	Good	1-5,000±	1-100:4	1-100+	Good
308	42	8	1-5,000±	1-500:5	.....	50%	1-5,000+	1-100:3	1-100+	75%
309	37	9	1-1,000+	1-500:8	.....	Good	1-5,000±	1-100:3	1-100±	Good
310	3	10	1-5,000±	1-500:3	.....	Good	1-5,000+	1-500:4	.....	Good
311	20	25	1-5,000±	1-100:4	.....	None	1-5,000±	1-100:1	.....	None
312	6	26	1:5,000+	1-100:1	.....	Good	1-5,000±	1-100:5	1-500	Good
314	3	11	1-5,000±	1-500:7	.....	75%	1-10,000±	1-500:4	.....	None
315	13	3	1-5,000±	1-500:4	.....	50%	1-10,000±	1-500:3	.....	Fair
316	34	9	1-5,000+	1-500:7	.....	75%	1-5,000+	1-100:2	.....	None
317	37	4	1-1,000±	1-500:2	.....	50%	1-1,000+	1-500:4	1-100±	75%
318	12	2	1-5,000±	1-500:2	.....	50%	1-5,000±	1-100:4	1-100±	75%
319	13	16	1-1,000+	1-500:5	.....	Fair	1-1,000+	1-500:2	.....	75%
320	29	6	1-5,000±	1-100:4	.....	None	1-10,000±	1-100:3	.....	50%
321	23	4	1-1,000+	1-500:6	.....	75%	1-5,000±	1-500:4	1-100.0	75%
			Season 1919				Season 1920			
322	32	10	1-5,000+	1-100:4	1-100±	Good	1-5,000±	1-500:3	.....	75%
323	39	5	1-10,000±	1-100:4	1-100+	Fair	1-5,000+	1-100:1	1-500±	75%
324	29	4	1-5,000+	1-100:4	1-100+	Good	1-5,000±	1-500:5	.....	75%
325	..	..	1-1,000±	1-100:4	1-100+	Fair	1-1,000+	1-500:3	.....	75%
326	50	2	1-5,000±	1-100:5	1-500±	Good	1-1,000+	1-100:2	1-500±	75%
327	..	..	1-10,000±	1-100:5	1-500+	Good	1-10,000±	1-500:5	.....	Good
328	18	3	1-5,000±	1-500:5	1-100±	Good	1-5,000±	1-100:2	.....	75%
329	..	..	1-5,000±	1-500:5	.....	Good	1-5,000±	1-100:3	.....	Fair
330	34	10	1-5,000+	1-100:5	1-100.0	None	1-1,000±	1-100:3	.....	75%
331	14	7	1-10,000±	1-500:5	.....	50%	1-10,000±	1-100:3	.....	75%
332	12	9	1-5,000±	1-500:5	.....	Fair	1-1,000±	1-500:5	.....	75%
333	4	12	1-10,000±	1-500:5	.....	75%	1-10,000±	1-500:5	.....	Fair
334	10	7	1-10,000±	1-100:2	1-500±	Fair	1-10,000±	1-500:4	.....	Fair
335	19	12	1-5,000±	1-500:4	.....	75%	1-5,000+	1-100:1	1-5,000±	50%
336	32	12	1-10,000±	1-100:3	1-500±	75%	1-10,000±	1-500:4	.....	50%
337	17	25	1-20,000±	1-100:2	.....	Good	1-10,000±	1-100:1	1-500±	Fair
338	..	36	1-10,000±	1-500:6	.....	Good	1-5,000+	1-500:5	.....	Fair
339	32	10	1-10,000±	1-100:4	1-100+	Fair	1-5,000±	1-100:3	.....	75%
340	..	25	1-10,000+	1-500:4	.....	Fair	1-5,000±	1-500:5	.....	75%
341	30	15	1-5,000+	1-500:6	1-100.0	75%	1-5,000+	1-500:2	.....	50%
342	30	4	1-10,000+	1-100:2	1-500+	Fair	1-10,000±	1-500:4	.....	50%
343	32	6	1-20,000±	1-100:3	1-500±	Fair	1-10,000±	1-500:4	.....	Fair
344	5	2	1-10,000±	1-100:2	.....	Good	1-1,000±	1-100:2	.....	Good
345	4	34	1-10,000±	1-100:2	1-500±	75%	1-5,000±	1-100:2	1-500±	Fair
346	6	4	1-10,000±	1-500:4	1-500±	75%	1-5,000±	1-500:6	1-500.0	75%
347	14	5	1-5,000±	1-500:6	1-500+	Fair	1-5,000±	1-500:5	1-500+	50%
348	16	45	1-10,000±	1-500:2	1-1,000+	50%	1-10,000±	1-500:5	1-1,000+	Fair
349	28	10	1-10,000±	1-500:6	.....	Good	1-5,000+	1-500:6	.....	Fair
350	27	6	1-10,000±	1-100:4	1-100+	Fair	1-5,000+	1-500:5	.....	50%
351	5	19	1-10,000±	1-500:3	.....	75%	1-10,000±	1-1000.1	.....	Fair
352	18	5	1-10,000+	1-500:4	1-500±	75%	1-5,000±	1-500:4	.....	75%
353	27	7	1-20,000±	1-100:3	1-500±	Fair	1-10,000±	1-500:3	.....	75%
354	38	4	1-5,000±	1-100:4	1-500±	Fair	1-5,000±	1-100:1	1-500+	Fair
355	34	12	1-10,000±	1-500:5	.....	75%	1-5,000±	1-500:5	.....	75%
356	28	6	1-20,000±	1-500:4	.....	Good	1-5,000±	1-500:5	.....	Fair
357	5	36	1-10,000±	1-100:1	1-500±	50%	1-5,000±	1-500:5	.....	Fair
358	28	13	1-10,000±	1-500:5	1-500±	50%	1-20,000±	1-500:4	.....	50%
359	..	28	1-20,000+	1-500:1	.....	50%	1-20,000+	1-500:5	1-1,000+	75%
360	23	39	1-20,000±	1-100:5	1-500±	Fair	1-10,000±	1-100:3	.....	Fair
361	45	7	1-1,000±	1-100:1	1-100+	Good	1-5,000±	1-500:4	1-500.0	75%
362	29	9	1-5,000±	1-500:5	1-500+	50%	1-10,000±	1-500:5	.....	75%
363	18	10	1-10,000±	1-500:4	1-500±	Good	1-5,000±	1-500:5	.....	Fair
364	27	30	1-10,000±	1-500:4	.....	75%	1-5,000+	1-500:5	.....	75%
365	31	28	1-5,000±	1-500:3	.....	Fair	1-5,000±	1-500:3	.....	50%
366	25	3	1-10,000+	1-500:4	1-500+	50%	1-10,000±	1-500:6	1-500+	75%
367	33	5	1-1,000±	1-100:4	1-100.0	Good	1-500±	1-500:4	.....	75%
313	1	3	1-5,000+	1-500:5	.....	Good	1-5,000±	1-100:2	.....	Good
368	40	18	1-10,000±	1-100:1	1-100±	Good	1-5,000+	1-500:5	.....	75%
369	11	8	1-5,000+	1-500:5	1-500±	Fair	1-5,000±	1-500:5	.....	75%
370	14	18	1-5,000±	1-100:4	1-100±	Good	1-500±	1-100:2	1-100±	75%
371	32	31	1-10,000+	1-100:4	1-100+	Good	1-5,000±	1-100:2	1-500±	75%
372	7	6	1-10,000±	1-100:1	1-100±	50%	1-5,000±	1-500:6	.....	75%

not benefited. For the second year of treatment, the results were: Of the seventy-three patients, twelve, or 16.4 per cent., were free from symptoms; sixteen, or 22 per cent., were practically free; thirty-three, or 45 per cent., were 75 per cent. relieved; nine, or 12 per cent., were 50 per cent. relieved, and three, or 4 + per cent., were not benefited. On comparing the results obtained from the first year's treatment with those obtained from the second year's treatment, it is noted that the same number of patients were practically free from symptoms both years, and that the number who were 50 per cent. benefited were about the same for the year, but that there were 57 per cent. more all right the first year than the second year, and 57 per cent. more that were 75 per cent. benefited the second year than the first.

Although the above results obtained by the first and second years' treatment do not differ markedly, yet this difference shows rather poorer results from the second year's treatment than from the first year's treatment, the opposite of what one would expect and desire. By comparing the amount of treatment that was given the first year with that given the second year it is evident that a diminished amount of treatment during the second year would seem to explain the poorer results obtained during this year, and it may be stated, that, as a rule, it is desirable to give as much treatment with the final dilutions the second year, provided sufficient treatment is given the first year, and sometimes less treatment is required.

Attention should be called to the few patients in Table 4 who were not benefited by treatment. Patient 311 was treated four times with the 1 : 100 dilution of pollen extract the first year, and once with the same dilution the second year, and yet there was no benefit from treatment either year; although this patient was much worse during August and September, he did have symptoms throughout the year so that it is probable that there was some cause of hay-fever besides ragweed pollen. It is difficult to undestand why Patient 314 should be 75 per cent. benefited following seven treatments with a 1 : 500 dilution of pollen extract the first year and not benefited by four similar treatments the second year unless the failure was due to insufficient treatment the second year. There is no evident reason why Patient 316, who was similarly treated both years, was 75 per cent. benefited the first year and not benefited the second year; neither is there an evident explanation why Patient 320, who was similarly treated both years, was not benefited the first year even though at the end of treatment the skin test was negative with a 1 : 100 dilution of the pollen, but was 75 per cent. benefited the second year. It happens that all of these failures occurred during the two years 1918 and 1919, and both ragweed seasons, as already described, were very similar. None of these patients were sensitive to pollens other than ragweed.

Fifty-seven skin tests were done at the end of treatment. In one case (335) the test was the same at the end of treatment as before treatment, and the patient was only 50 per cent. benefited; a similar instance was noted in Table 1. Patient 348 gave a positive skin test with a 1 : 1,000 dilution of the pollen extract both years at the end of treatment, but was 50 per cent. benefited the first year and was practically free from symptoms the second year. In the remaining fifty-four tests, there was the usual diminished intensity of the reaction; in one third of the cases, or those who had been treated with the 1 : 100 dilution of pollen extract, the skin test was positive in no dilution higher than 1 : 100, and in some cases even this dilution was negative; in the remaining two-thirds of the instances no dilution higher than 1 : 500 gave a positive skin test at the end of treatment. The sensitivity of the patients was decreased from ten to one hundred times with an average decrease of from twenty to fifty times.

The conclusions resulting from Table 4 substantiate all of those already mentioned, and the conclusion that one or more treatments with a 1 : 100 dilution produces the best results and the greatest reduction in the intensity of the skin test is likewise confirmed.

In Table 5 are presented seven cases of early hay-fever treated two years in succession. During 1918 and 1919, three patients were treated with grass pollen; during 1919 and 1920 three patients were treated with grass pollen, and during 1917 and 1918 one patient was treated with rose pollen.

Patient 374, who was treated three times with a 1 : 500 dilution of timothy pollen extract, was 75 per cent. benefited; what symptoms this patient had were present chiefly in early June. The second year, although it was found that this patient was as sensitive to the pollen of June grass as to timothy, it was decided to treat him more strenuously with timothy pollen extract again since the first year's treatment with timothy was not deemed sufficient. Following two treatments with the 1 : 100 dilution of timothy pollen extract the second year, he was again 75 per cent. benefited and again his chief symptoms were manifested in June. Therefore, it is quite evident that since his chief symptoms were manifested in early June, previous to timothy pollination and during the pollination of June grass, to which he was very sensitive, that June grass was the cause of the symptoms, and that although timothy treatment had not protected against June grass, it was really successful as far as timothy was concerned. During a third year, 1920, he was treated only with June grass pollen extract and had no symptoms during June grass pollination, but he did have considerable trouble during late June and July. In order to simplify the table this treatment is omitted. Therefore, there is no question that during the 1918 and 1919 seasons his 25 per cent. of symptoms were caused by June

TABLE 5.—Preseasonal Tests and Treatment with Grass Pollens Two Successive Years

Patient	Duration	Age of Onset	Season 1918								Season 1919							
			Tests Before Treatment			No. Treatments With Final Dilution, Timothy	Tests at End of Treatment			Result of Treatment	Tests Before Treatment			No. Treatments With Final Dilution		Tests at End of Treatment			Result of Treatment
			Timothy	Red Top	June Grass		Timothy	Red Top	June Grass		Timothy	Red Top	June Grass	Timothy	June Grass	Timothy	Red Top	June Grass	
374	1	47	1-5,000+	1-500+	.....	1-500:3	.....	.....	.....	75%	1-5,000±	1-1,000±	1-5,000±	1-100:2	.....	1-500±	1-1,000±	1-1,000±	75%
375	19	10	1-5,000±	1-500+	.....	1-500:4	.....	.....	.....	75%	1-1,000+	1-1,000±	1-500±	1-500:4	.....	.....	.....	.....	75%
376	22	12	1-5,000±	1-5,000±	.....	1-500:4	.....	.....	.....	Good	1-1,000±	1-1,000±	1-500±	1-100:3	.....	1-100±	1-100+	1-100+	Good
					Season 1919										Season 1920				
377	11	8	1-5,000±	1-500+	1-100±	1-100:1	1-100+	.....	.....	Good	1-5,000±	1-500±	1-5,000±	1-500:4	1-1,000:2	.....	.....	.....	75%
378	25	3	1-5,000±	1-1,000±	1-500±	1-100:5	1-100±	1-500±	1-100±	Good	1-5,000+	1-5,000±	1-5,000±	1-500:4	1-500:1	.....	.....	.....	75%
379	11	3	1-5,000±	1-500+	1-5,000±	1-100:3	.....	.....	.....	Good	1-5,000±	1-1,000+	1-5,000±	1-500:5	1-1,000:3	.....	.....	.....	50%
					Season 1917										Season 1918				
373	21	3	Rose 1-1,000+	—	—	Rose 1-500:5	.....	.....	.....	Good	Rose 1-1,000±	.....	.....	Rose 1-500:6	.....	.....	.....	.....	Good

grass pollen and that his timothy pollen treatment was successful. Patient 375 was treated four times each year with a 1:500 dilution of timothy pollen alone and was 75 per cent. benefited. Since this patient was not very sensitive to June grass and had no symptoms until timothy pollination, it is evident that he had, as already shown, insufficient timothy treatment. Patient 376 was chiefly sensitive to timothy pollen and was free from symptoms following treatment with timothy pollen extract.

Patients 377 and 378 were chiefly sensitive to timothy pollen extract the first year and were free from symptoms following treatment with timothy pollen alone. The second year they were equally sensitive to the pollens of both June grass and timothy, and were given less treatment than the preceding year with timothy pollen and a little treatment with June grass pollen extract; they were only 75 per cent. benefited the second year and their symptoms were manifested chiefly in late June and July. Therefore, treatment with the two pollen extracts together diminished the amount of treatment that they might have had with timothy alone, and the result was that both patients were only 75 per cent benefited the second year; furthermore, it is evident that they did not need June grass pollen treatment anyway. The case of Patient 379 was similar to the two cases just discussed, with the exception that this patient was equally sensitive to both pollens the first year as well as the second year, and that she was only 50 per cent. benefited the second year by treatment similar to that given the two cases just cited; the fact that this patient began treatment late, thus necessitating a five day interval between treatments, may partly explain the poor results.

Patient 373 was sensitive to the pollen of rose alone, and five and six treatments in 1917 and 1918, respectively, prevented any symptoms both years even though, since she was a nurse in a hospital, she had to be exposed freely to roses. Incidentally, it should be stated that previous to treatment, whenever she scratched her hands on rose thorns, marked itching and swelling resulted at the points of injury, but following rose pollen treatment these symptoms did not occur when injured by rose thorns.

The conclusions to be drawn from Table 5 verify those already proven correct in Table 2. The important conclusions are, that treatment with two pollens together is not advisable; that the early type of hay-fever is chiefly due to timothy pollen, and sufficient treatment with timothy pollen alone, namely, treatment with the 1:100 dilution or its equivalent of a 1:500 dilution, will give satisfactory results in such cases; that this amount of treatment will usually markedly diminish the intensity of the skin test to timothy pollen, and that only an occasional case of early hay-fever is due to rose pollen. The correctness of

TABLE 6.—Preseasonal Tests and Treatment with Ragweed Pollen Three Successive Years

Patient	Age of Onset	Duration	Season 1917			Season 1918				Season 1919			
			Tests Before Treatment	Number Treatments With Final Dilution	Result of Treatment	Tests Before Treatment	Number Treatments With Final Dilution	Tests After Treatment	Result of Treatment	Tests Before Treatment	Number Treatments With Final Dilution	Tests After Treatment	Result of Treatment
381	38	11	1-1,000±	1-100:1	Good	1-1,000±	1-100:4	.....	Fair	1-1 000±	1-500:4	.....	Fair
382	15	17	1-10,000±	1-500:3	75%	1-10 000±	1-500:3	.....	75%	1-10 000±	1-500:3	.....	75%
283	20	10	1-5 000±	1-100:3	Good	1-5 000±	1-500:5	.....	75%	1-5 000±	1-500:5	.....	75%
384	32	10	1-1,000±	1-100:2	Good	1:1,000±	1-500:4	.....	Good	1-10 000±	1-500:5	.....	Fair
385	25	8	1-1 000±	1-100:3	Good	1-1 000±	1-100:1	.....	Good	1-10 000±	1-500:5	.....	Fair
			Season 1918			Season 1919				Season 1920			
386	9	3	1-1,000±	1-500:3	Good	1-500±	1-100:6	1-100.0	Good	Pol +	1-500:7	.....	Fair
387	21	5	1-10,000±	1-100:1	75%	1-10 000±	1-100:2	1-100+	Fair	1-5,000+	1-500:5	1-500±	Fair
388	28	15	1-5,000±	1-500:3	50%	1-5,000±	1-100:2	1-100+	Good	1-10,000±	1-500:4	.....	75%
389	..	23	1-5,000±	1-500:3	75%	1-5,000±	1-100:4	1-100+	Good	1-1,000±	1-500:5	.....	Fair
390	17	2	1-1,000±	1-500:2	50%	1-5 000±	1-100:5	1-100±	Fair	1-5 000±	1-500:4	.....	75%
391	1	34	1-5,000+	1-500:5	75%	1-5 000+	1-500:6	.....	Fair	1-5,000±	1-500:5	.....	Fair
392	20	20	1-5 000+	1-100:2	75%	1-10,000+	1-100:3	1-100+	Good	1-5,000+	1-500:5	1-1,000+	75%
393	27	5	1-5,000±	1-500:3	75%	1-5,000±	1-100:3	1-100.0	Good	1-1,000+	1-500:5	.....	75%
394	12	20	1-5,000±	1-500:4	Good	1-5,000±	1-100:1	1-500±	Fair	1-5,000±	1-500:4	1-1,000+	50%
395	11	39	1-5.000±	1-500:3	75%	1-5 000+	1-500:3	1-500+	75%	1-5,000±	1-500:6	.....	Fair
396	21	19	1-5 000+	1-500:4	Good	1-5,000+	1-500:4	1-1,000+	Fair	1-1,000+	1-100:2	.....	Fair
397	24	20	1-5,000±	1-500:4	Fair	1-5,000±	1-100:5	1-100+	Good	1-5,000+	1-500:4	.....	75%
398	28	10	1-5,000±	1-500:5	75%	1-5,000±	1-500:5	.....	50%	1-5,000±	1-500:4	.....	50%
399	30	25	1-10.000±	1-500:6	50%	1-5,000+	1-500:3	1-500+	75%	1-20,000+	1-500:5	1-500+	Fair
400	24	10	1-5,000±	1-500:4	50%	1-5,000±	1-100:5	1-100+	75%	1-5 000±	1-500:5	.....	75%
401	33	16	1-5.000±	1-500:2	50%	1-5,000±	1-500:5	1-100+	75%	1-5,000±	1-100:1	1-100+	75%
402	26	8	1-10,000±	1-500:3	75%	1-10,000±	1-200:2	1-100+	Fair	1-5.000±	1-100:1	1-500+	75%
403	16	2	1-10.000±	1-500:2	50%	1-10 000±	1-500:5	.....	75%	1-10 000±	1-100:2	.....	Good
404	36	6	1-1.000+	1-100:4	Good	1-1 000+	1-100:4	.....	Good	1-1 000+	1-100:4	.....	Good
405	8	22	1-1,000+	1-100:1	Good	1-1,000±	1-500:4	.....	Good	1-500±	1-500:6	1-100.0	Good

the conclusion drawn from Table 4 that usually the patient needs as much treatment with the final dilutions the second year as he received the first year is also proven.

In Table 6, twenty-five patients, who were treated three years in succession with ragweed pollen extract, are presented. During 1917 to 1919 inclusive, five patients were treated, and during 1918 to 1920 inclusive, twenty were treated.

Analysis of Table 6 shows that following the first year of treatment, a third of the patients were free from symptoms; one patient, or 4 per cent., was practically free; a third was 75 per cent. benefited, and six patients, or 24 per cent., were 50 per cent. benefited. Following the second successive year's treatment, ten patients, or 40 per cent., were free from symptoms; seven, or 28 per cent., were practically free; seven, or 28 per cent., were 75 per cent. benefited, and one patient, or 4 per cent., was 50 per cent. benefited. Following the third successive year's treatment, three patients, or 12 per cent., were free from symptoms; ten, or 40 per cent., were practically free; ten, or 40 per cent., were 75 per cent. benefited, and two, or 8 per cent., were 50 per cent. benefited. There were no failures in any year. Seven of the twenty-five patients were either entirely free or practically free from symptoms all three years.

A comparison of the results of the three years' treatments with the amount of treatment given to each patient each year substantiates previous conclusions: (1) Treatment with the 1 : 100 dilution yielded by far the best results; (2) five or six doses of the 1 : 500 dilution was followed by excellent results; (3) three or four doses of the 1 : 500 dilution sometimes was followed by excellent results but more often by 75 per cent. benefit, and (4) two doses of the 1 : 500 dilution gave poor results.

In twenty-two instances skin tests were done at the end of treatment. Following treatment with the 1 : 100 dilution of pollen protein, in two instances the 1 : 100 dilution was negative; in nine instances the 1 : 100 dilution gave a doubtful to a positive reaction, and in only two instances was the 1 : 500 dilution at all positive. Following treatment with the 1 : 500 dilution, in one instance the 1 : 100 dilution was somewhat positive; in four instances the 1 : 500 dilution was more or less positive, and in three instances the 1 : 1,000 dilution was positive. Two of those that were positive with the 1 : 1,000 dilution were treated four times with the 1 : 500 dilution, and two of those that were positive with the 1 : 500 dilution were given only three doses of the 1 : 500 dilution. Therefore, as shown repeatedly, there is nearly always a great decrease in the sensitivity of the patient, as evidenced by the skin test, following considerable treatment, and the greatest decrease results from treatment with the 1 : 100 dilution.

TABLE 7.—Preseasonal Tests and Treatment with Grass Pollens Three Successive Seasons

Patient	Age of Onset	Duration	Season 1918				Season 1919					Season 1920					
			Tests Before Treatment		No. Treatments With Final Dilution, Timothy	Result of Treatment	Tests Before Treatment			No. Treatments With Final Dilution, Timothy	Result of Treatment	Tests Before Treatment		No. Treatments With Final Dilution			Result of Treatment
			Timothy	Red Top			Timothy	Red Top	June Grass			Timothy	Red Top	June Grass	Timothy	June Grass	
410	22	25	1-5,000±	1-1,000+	1-500:3	Fair	1-5,000+	1-5,000±	1-1,000±	1-100:4	Good	1-1,000±	1-1,000+	1-1,000±	1-100:3	1-100:3	50%
411	23	10	1-10,000±	1-5,000±	1-500:5	Good	1-10,000±	1-5,000±	1-1,000±	1-100:4	Good	1-5,000±	1-1,000+	1-1,000+	1-100:4	1-500:6	75%
412	..	..	1-500+	1-100±	1-500:6	Fair	1-500±	1-500±	1-100±	1-100:3	Good	1-100±	1-100±	1-100.0	1-500:5	1-500:6	Good
413	15	45	1-1,000±	1-100+	1-100:3	Good	1-500+	1-500±	.....	1-100:1	Good	1-500±	1-500±	1-100.0	1-100:2	.....	Good

In Table 7 are presented four patients with early hay-fever who were treated three years in succession with the grass pollens. The four patients were either free or practically free from symptoms following treatment with timothy pollen alone the first year, and all were entirely free from symptoms following an increased amount of timothy pollen treatment the second year, even though two of the patients were equally sensitive to redtop pollen and quite sensitive to June grass pollen. Therefore, as already proven, timothy pollen treatment will protect against redtop pollen and there was no evidence that the patients needed June grass pollen treatment. From the experience of the first two years, there was every reason to believe that similar timothy pollen treatment alone would ensure excellent results the third year. Therefore, it was decided to make an experiment of these four cases by treating three of them with varying amounts of June grass pollen together with sufficient timothy treatment, and to treat the fourth patient with timothy pollen alone as a control. The results were interesting, in that the first patient who had the maximum treatment with both pollen extracts was only 50 per cent. benefited; the second patient who had maximum treatment with timothy pollen, and considerable, though less, treatment with June grass pollen, was 75 per cent. benefited, whereas the third patient, who had considerable, though less, treatment with timothy pollen than the other two patients, but who had as much treatment with June grass pollen, was free from symptoms, and the fourth patient, following treatment with timothy pollen extract alone, was also free from symptoms. Therefore, the only difference in the treatment of the first three cases between the first two years and the third year was the additional treatment with June grass pollen in the third year. The greater the amount of treatment with June grass pollen extract, the poorer were the results, and the same number of treatments with June grass pollen in a nonsensitive case and no June grass treatment in a nonsensitive case was followed by excellent results. In order to give the first patient three treatments with the 1 : 100 dilution of pollen extract, this treatment was carried on in increasing large doses during June grass pollination so that the patient was being treated by and at the same time was being exposed to June grass pollen, and the result was that the patient had much hay-fever during June as a result of treatment with large doses of June grass pollen at the time of natural exposure to the pollen, although in the previous two years he either was not sufficiently exposed to June grass pollen or he had sufficient protection against it. The second patient was comparable with the first, with the exception that the June grass pollen treatment was discontinued shortly after the onset of June grass pollination, but timothy pollen treatment was continued as in the first case. Therefore, the second case had less treatment during June grass pollination and

TABLE 8.—Preseasonal Tests and Treatment with Ragweed Pollen Four Successive Years

Patient	Age of Onset	Duration	Season 1917			Season 1918			Season 1919			Season 1920		
			Tests Before Treatment	Number Treatments With Final Dilution	Result of Treatment	Tests Before Treatment	Number Treatments With Final Dilution	Result of Treatment	Tests Before Treatment	Number Treatments With Final Dilution	Result of Treatment	Tests Before Treatment	Number Treatments With Final Dilution	Result of Treatment
406	5	42	1-1,000±	1-100:4	Good	1-100+	1-100:4	75%	1-50+	1-100:4	75%	1-500±	1-100:3	75%
407	31	16	1-1,000±	1-100:3	75%	1-1,000±	1-500:4	Fair	1-1,000±	1-100:2	Good	1-1,000+	1-500:4	Fair
408	21	29	1-5,000±	1-100:3	Fair	1-5,000±	1-500:5	50%	1-5,000±	1-500:5	75%	1-10,000±	1-500:6	75%
409	15	45	1-5,000±	1-500:3	50%	1-5,000±	1-500:5	Fair	1-5,000±	1-500:2	None	1-10,000+	1-500:5	Good

had less symptoms in June so that the result was 75 per cent. benefit. The third patient had as much June grass treatment but was not sensitive to June grass pollen, therefore, June grass treatment during its pollination was harmless and needless as it would have been had it been given to the fourth patient.

The manner in which June gross pollen was given to the patients in Table 7 differs from the way it was given in the preceding tables in that in these cases treatment with June grass was discontinued before the onset of its pollination, whereas, the patients in Table 7 were treated with gradually increasing amounts of June grass pollen during the time the patients were being naturally exposed to the pollen. Therefore, treatment with large amounts of a pollen extract during the season of its pollination is evidently not desirable. The conclusion that has already been repeatedly stated, namely, that mixed pollen treatment is, as a rule, not only unnecessary but undesirable, was equally true of cases in Table 7, and the poorer results obtained in the third successive year of treatment was due, as shown repeatedly, to mistreatment.

In Table 8 are presented four patients who were treated with ragweed pollen extract four successive years.

They illustrate the slightly variable results that may be obtained by giving similar treatment each year to the same patient for several years, and by giving varying amounts of treatment to the same patient for several years.

In three of these cases the results expressed on a percentage basis were practically identical for all four years and the only exception to this in the fourth patient was the unfavorable result that followed too little treatment in the third year. In other words, favorable results may be looked for following any number of successive years' treatment, provided the average number of treatments are given each year. No matter how many successive years the same patient is treated, as a rule, approximately the same amount of treatment with the final dilution is required each year as that which gave desirable results any preceding year, however, no greater amount of treatment is required in successive years than that which gave desirable results any preceding year.

During-the-Season or Curative Treatment with Pollen.—Frequently patients present themselves for treatment during their hay-fever attack, and although pollen treatment at this time does not seem to be very logical, on the basis of anaphylaxis, the patient often will insist on taking the chance. Pollen treatment during the season does not seem logical because the patient is being injected with the pollen which is causing symptoms at the same time that he is being exposed to the pollen present in the air which he is inhaling. The danger resulting from large doses of the injected pollen is obvious because of an over-

dose, due to the combination of the injected pollen and the inhaled pollen. Therefore, in order that during-the-season treatment should be beneficial, the patient must be injected with minute amounts of the pollen extract in order to diminish artificially a few of the patients antibodies, thus leaving a smaller number of antibodies in the patient for combination with the pollen antigen that is inhaled. If too much pollen extract (antigen) is injected, the patient should have symptoms due to over-treatment alone, or he should be made worse, due to the injection of pollen extract (antigen) superimposed on the inhalation of pollen (antigen). It is evident, that on the basis of anaphylaxis, during-the-season treatment is hazardous, and although the skin test is the best guide as to the proper treatment, there is no way of controlling the amount of pollen that the patient may inhale.

TABLE 9.—Test and Treatment During Season With Grass Pollen

Patient	Previous No.	Tests Before Treatment. Timothy	Dates of Treatment	Treatment in Cubic Centimeters With Dilution of Timothy Pollen	Result of Treatment
Season 1917					
415	374	1-20,000±	6/22 to 7/12	1-20,000 = 0.15, 0.3; 1-10,000 = 0.15, 0.15	75%
424	...	1-1,000±	6/20 to 6/29	1-1,000 = 0.15; 1-500 = 0.1, 0.15	50%
416	...	1-5,000+	6/22 to 7/14	1-10,000 = 0.15; 1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15	25%
Season 1919					
440	...	1-5,000±	7/10 to 7/24	1-10,000 = 0.15; 1-5,000 = 0.15, 0.3	25%
441	...	1-1,000+	6/10 to 7/14	1-5,000 = 0.1, 0.15, 0.3, 0.45; 1-1,000 = 0.15, 0.3	None
443	...	1-5,000±	6/16 to 7/10	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3, 0.45	Fair
444	...	1-1,000+	6/19 to 7/14	1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15, 0.3	Fair
445	308	1-1,000±	6/ 5 to 7/ 5	1-5,000 = 0.15, 0.3; 1-1,000 = 0.1, 0.15, 0.3, 0.45	75%
446	206 286	1-1,000±	6/16 to 7/14	1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15, 0.3	75%
442	...	J. G. 1-500±	5/30 to 6/20	J. G. 1-1,000 = 0.15, 0.3; 1-500 = 0.15, 0.3	None
Season 1920					
452	...	1-10,000±	6/15 to 7/ 6	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3, 0.4	Fair
455	...	1-100+	6/24 to 7/14	1-1,000 = 0.15, 0.3, 0.3, 0.4, 0.45	75%
456	...	1-10,000±	6/21 to 7/10	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3, 0.45	50%
457	...	1-5,000±	6/26 to 7/17	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3, 0.45	50%
458	...	1-5,000+	6/26 to 7/17	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3, 0.45	None
459	...	1-5,000±	6/24 to 7/17	1-10,000 = 0.15, 0.3, 0.45, 0.55, 0.65	Fair
460	...	1-5,000±	6/26 to 7/17	1-10,000 = 0.15, 0.3, 0.45, 0.55	None
461	...	1-1,000+	6/26 to 7/17	1-5,000 = 0.15, 0.3, 0.45, 0.55	25%
462	...	1-5,000+	6/22 to 7/17	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3	None
451	...	T. and J. G. 1-5,000±	6/12 to 7/ 1	T. and J. G. 1-10,000 = 0.15, 0.3, 0.3, 0.45	Fair
453	...	1-5,000±	5/29 to 6/22	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3, 0.4	Fair
454	...	J. G. 1-100+	5/29 to 6/16	J. G. 1-1,000 = 0.15, 0.3, 0.45	Fair

In Table 9 are presented twenty-two patients who were treated with grass pollens during the season of their pollination, and while they were having symptoms from exposure to these pollens. Three patients were treated in 1917 with timothy pollen; in 1919, six were treated with timothy, and one was treated with June grass, and in 1920, nine were treated with timothy, two with the combination of timothy and June grass, and one with June grass alone.

Before considering Table 9, it may be well to explain the notations beneath the headings of each column, using the first patient as an example. Four hundred and fifteen is the sequence number of the patient in the whole series presented in this paper. No. 374 in the second column means that this same patient has been presented previously in this paper, and on referring back, it is seen that this patient was presented in Table 5 which consisted of patients who were treated with grass pollen two years in succession; in other words as No. 415 the patient was treated during the season in 1917 (Table 9) and preseasonally two successive years, 1918 and 1919 (Table 5). The third column gives the skin test. The next column gives the dates of treatment, that is June 22 to July 12, inclusive. The treatment column gives the dilutions with which the patient was treated and the respective amounts of each treatment dilution in cubic centimeters; for instance 1:20,000 dilution of timothy pollen extract, dose 0.15 c.c., then 0.3 c.c., after this the 1:10,000 dilution, dose 0.15 and 0.15 c.c. The five or seven day interval between doses is understood, and usually the same scheme of treatment was followed as outlined in the first part of this paper for preseasonal treatment, and the skin test was used as the guide to determine the initial dose. The last column gives the result from during-the-season treatment, for instance, the first patient was 75 per cent. benefited.

The results from during-the-season treatment were: Of the twenty-two patients treated, none were free from symptoms; seven, or 32 per cent., were practically free; four, or 18 + per cent., were 75 per cent. benefited; three, or 13 + per cent., were 50 per cent. benefited; the same number were 25 per cent. benefited, and five, or 22 + per cent., were not benefited. Since no patients were entirely relieved of symptoms, and since a large percentage were not benefited, it is evident, on comparing these results with those of former tables, that preseasonal treatment ensures better results by far than does during-the-season treatment. If preseasonal treatment is absolutely barred, during-the-season treatment is worth trying, provided it is given with sufficient care and the skin test is used as a guide to the initial treatment.

Patients 442 and 454 were treated with June grass (J. G.) alone because they were sensitive to this pollen only, and were having symptoms during June grass pollination, as noted by the dates of treatment, namely, from the last of May to the middle of June. Patients 451 and 453 were treated with the combination of timothy and June grass pollen extracts because they were having symptoms and were sensitive to June grass, and they were also sensitive to and had had symptoms during the timothy pollination. The other patients were treated with timothy pollen extract alone because practically all of them were first seen at the end of June grass pollination and at the beginning or during timothy pollination.

With three of the patients we have the opportunity of contrasting during-the-season treatment with preseasonal treatment. Patient 415 was 75 per cent. benefited by during the season treatment, and he was similarly benefited by preseasonal treatment in the two following years (Table 5, Patient 374). Patient 445, who was 75 per cent. benefited by during-the-season treatment, was free from symptoms following preseasonal treatment (Table 2, Patient 208). Patient 446, who was 75 per cent. benefited from during-the-season treatment, was similarly benefited following preseasonal treatment (Table 2, Patient 205), and was not benefited following the same amount of preseasonal treatment (Table 3, Patient 286) as was given during the season. It is not advisable to draw general conclusions from these three cases, although they are of sufficient interest to warrant mention.

TABLE 10.—Test and Treatment During Season with Ragweed Pollen

Patient	Previous No.	Tests Before Treatment	Dates of Treatment	Treatment in Cubic Centimeters With Dilution of Ragweed Pollen	Result of Treatment
Season 1917					
417	35a	1-1,000+	8/14 to 9/28	1-1,000 = 0.15, 0.2, 0.3, 0.4, 0.45, 0.5	75%
418	...	1-5,000±	9/ 4 to 9/27	1-10,000 = 0.15; 1-5,000 = 0.15; 1-1,000 = 0.15	75%
419	36	1-5,000+	8/27 to 9/ 4	1-10,000 = 0.15, 0.3	Fair
420	...	1-5,000±	9/ 6 to 9/24	1-10,000 = 0.15; 1-5,000 = 0.15, 0.3, 0.45	50%
421	...	1-1,000±	8/10 to 9/ 5	1-5,000 = 0.15; 1-1,000 = .15, .3; 1-500 = 0.15, 0.3, 0.45	25%
422	119	1-10,000±	9/ 4 to 9/27	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3	None
423	...	1-5,000±	8/16 to 9/10	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3, 0.45	50%
Season 1918					
425	371	1-1,000+	8/17 to 8/29	1-5,000 = 0.15, 0.3, 0.45	None
426	372	1-1,000+	8/28 to 9/11	1-5,000 = 0.15, 0.15, 0.2	50%
427	6	1-10,000±	8/28 to 9/14	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3	50%
428	59	1-5,000±	8/22 to 9/ 5	1-10,000 = 0.15, 0.3, 0.3	50%
429	...	1-1,000+	8/20 to 9/14	1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15, 0.3	None
430	...	1-1,000±	8/16 to 9/ 7	1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15	50%
431	61	1-1,000+	8/29 to 9/13	1-5,000 = 0.15, 0.3, 0.45	None
432	346	1-1,000±	8/28 to 9/10	1-5,000 = 0.15, 0.3, 0.45	None
433	360	1-10,000±	8/13 to 8/30	1-20,000 = 0.15, 0.3; 1-10,000 = 0.15	None
434	84	1-1,000+	8/28 to 9/10	1-5,000 = 0.15, 0.3, 0.45	None
435	370	1-1,000+	8/20 to 9/13	1-5,000 = 0.15, 0.3, 0.4, 0.45, 0.5	Good
436	...	1-1,000±	8/16 to 9/24	1-5,000 = 0.15, 0.3, 0.45, 0.45; 1-1,000 = 0.15, 0.3, 0.3	Good
437	...	1-10,000±	8/14 to 9/ 9	1-20,000 = 0.15; 1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3	None
438	...	1-5,000±	8/20 to 9/10	1-10,000 = 0.15; 1-5,000 = 0.15, 0.15, 0.3	75%
439	184	1-5,000±	8/14 to 9/14	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15, 0.3, 0.45	None
447	10	1-10,000+	8/19 to 9/14	1-20,000 = 0.15, 0.3; 1-10,000 = 0.15, 0.3, 0.45	None
448	...	1-10,000±	9/ 1 to 9/21	1-20,000 = 0.15, 0.3; 1-10,000 = 0.15, 0.3	None
449	62	1-5,000±	8/29 to 9/11	1-10,000 = 0.15, 0.3; 1-5,000 = 0.15	None
450	...	1-10,000±	7/31 to 9/21	1-20,000 = 0.15, 0.3, 0.45, 0.55; 1-5,000 = 0.15, 0.3, 0.45, 0.55	50%
463	...	1-1,000+	8/20 to 9/20	1-5,000 = 0.15, 0.3, 0.45; 1-1,000 = 0.15, 0.3	Good

In Table 10 are presented twenty-seven patients who were treated with ragweed pollen extract during the season. The notations in this table are exactly like those in Table 9, therefore, no explanation is needed. It should be stated, however, that these patients were tested with and found to be either not sensitive or only slightly sensitive to other pollens.

Of the twenty-seven patients presented in Table 10, three, or 11 + per cent., were free from symptoms; one patient, or 3 + per cent., was practically free; three patients, or 11+ per cent., were 75 per cent. benefited; seven, or 25+ per cent., were 50 per cent. benefited; one patient, or 3+ per cent., was 25 per cent. benefited, and twelve patients, or 44+ per cent., were not benefited. Therefore, although a few patients were free from symptoms, and as many more were 75 per cent. benefited, the number who were only 50 per cent. benefited was as great as the number who were more than 50 per cent. benefited, and nearly half of the whole series were not benefited at all. On comparing these results from during-the-season treatment with the results presented in former tables from preseasonal treatment, it is evident that for late hay-fever by far the best results are obtained from preseasonal treatment, and it is questionable whether during-the-season treatment is even worth giving when it is taken into consideration that there are localities to which patients may go where ragweed does not exist.

Since fifteen of these patients have been discussed elsewhere in this paper, it is possible with these to compare during-the-season treatment with preseasonal treatment. Ten of the patients were presented in Table 1, therefore, it is possible to contrast the results from the two kinds of treatment in these cases with little detail. Patient 417 (35a) was free from symptoms following preseasonal treatment and 75 per cent. benefited from during-the-season treatment; Patient 419 (36) was free from symptoms following preseasonal and practically free from symptoms from during-the-season treatment; Patient 428 (59) was 50 per cent. benefited as a result of both kinds of treatment; therefore, in these three cases, the results from preseasonal treatment were slightly better than those from during-the-season treatment in two of them, and the same in the third case. The other seven cases in this group, namely, Patients 422 (119), 427 (6), 431 (61), 435 (84), 439 (184), 447 (10) and 449 (62) were not benefited by during-the-season treatment, but following preseasonal treatment three were free from symptoms, one was practically free, two were 75 per cent. benefited and the remaining patient was 50 per cent. benefited. Therefore, in these seven cases during-the-season treatment was a failure, whereas preseasonal treatment gave very satisfactory results. Since the remaining five patients in Table 10, that have been presented elsewhere, were all presented in Table 4, they may be considered together with little detail. Patient 426 (372) was 50 per cent. benefited by during-the-season treatment, and was 50 per cent. and 75 per cent., respectively, benefited the two seasons during which he was preseasonally treated; Patient 435 (370) was free from symptoms from during-the-season treatment and was free from symptoms and 75 per

cent. benefited the two respective seasons following preseasonal treatment; therefore, in these two cases, the results from both kinds of treatment were very similar. Patients 425 (371), 432 (346) were not benefited at all by during-the-season treatment, whereas following preseasonal treatment two successive years, Patient 425 (371) was free from symptoms and 75 per cent. benefited, Patient 432 (346) was 75 per cent. benefited both years. Patient 433 (369) was practically free and 75 per cent. benefited. With these three cases, therefore, during-the-season treatment was a failure, whereas preseasonal treatment was very satisfactory.

From these fifteen patients who were treated both ways it may be noted that frequently during-the-season treatment gives as good results as preseasonal treatment. This was true in five, or one third, of the cases. However, more often during-the-season treatment is a failure in the same cases in which preseasonal treatment is very satisfactory. This was true in ten, or two-thirds, of the cases. These conclusions also verify what was stated in the second preceeding paragraph, namely, that for late hay-fever by far the best results are obtained from preseasonal treatment than from during-the-season treatment.

In Table 11 are presented nineteen patients who were treated with bacterial vaccines during their hay-fever attack, although they were very sensitive to ragweed pollen and were having hay-fever symptoms during ragweed pollination. The reason for such treatment was that it is quite possible that ragweed pollen exposure may in some cases cause such a severe irritation of the mucous membranes that ever-present bacteria may, either alone or together with ragweed pollen, be a cause of hay-fever symptoms. In our study on pollen asthmatics [8] this was found to be the case in many instances, and Frank and Strouse,[9] Medalia,[10] Scheppegrell [11] and others, have considered this to be true in hay-fever cases. The construction of Table 11 differs from that of Tables 9 and 10 in only two ways, namely, that treatment was given with bacterial vaccines, and that the numerals under the treatment column represent that many hundred millions of bacteria per dose. In some instances, the vaccine used was an autogenous one made from the patient's nasal secretions; in other instances it was a stock vaccine consisting of *Staphylococcus pyogenous aureus* or *S. albus*, and for those patients who were treated in 1920, a mixed

8. Walker, I. C.: Sensitization and Treatment of Bronchial Asthmatics with Pollens, Am. J. M. Sc. **157**:409, 1919.

9. Frank, I., and Strouse, S.: Pollen Extracts and Bacterial Vaccines in Hay-Fever, J. A. M. A. **72**:1593 (May 31) 1919.

10. Medalia, L. S.: Hay-Fever; Its Treatment with Autogenous Vaccines and Pollen Extract, Boston M. & S. J. **175**:201, 1916.

11. Scheppegrell, W.: Anaphylaxis Due to Pollen Protein, with a Report of the Results of Treatment in the Hay-Fever Clinic of the New Orleans Charity Hospital, Laryngoscope **28**:853, 1919.

streptococcus vaccine was used. This mixed streptococcus vaccine consisted of equal amounts of the six streptococci that were most frequently found in the sputum and nasal secretions of asthmatic patients.[12] These streptococci, according to Holman's classification, were hemolytic types *S. pyogenes, S. infrequens* and *S. anginosus* and nonhemolytic types *S. salivarius, S. ignavus* and *S. mitis* in the proportion of approximately sixteen million of each per one hundred million of total, so that a dose of 300 million mixed streptococci represented about fifty millions of each of the six strains.

TABLE 11.—During Season Treatment with Bacteria

Patient	Previous No.	Skin Test With Ragweed	Dates of Treatment	Treatment With Vaccines	Each Treatment Recorded in Hundred Million	Result of Treatment
Season 1919						
464	184, 439	1-5,000±	8/30 to 9/15	Autog. nasal	3, 4, 5	Good
465	264, 181	1-10,000±	8/30 to 9/15	Staph. pyog. albus	3, 4, 5	None
466	...	1-5,000±	9/ 6 to 9/14	Autog. nasal	3, 4, 5	50%
467	272	1-5,000±	9/10 to 9/24	Autog. nasal	3, 4, 5	75%
468	11	1-10,000±	8/23 to 9/13	Staph. pyog. albus	3, 4, 5	None
469	...	1-10,000+	9/ 5 to 9/20	Autog. nasal	3, 4, 5	None
470	185	1-5,000±	8/23 to 9/12	Staph. pyog. aureus	3, 4, 5, 6	75%
471	385	1-1,000+	8/29 to 9/18	Autog. nasal and alb.	3, 4, 5, 6	None
472	187	1-10,000±	8/30 to 9/18	Autog. strept.	3, 4, 5, 6	Good
Season 1920						
473	463	1-1,000+	9/ 4 to 9/20	Mixed strept.	3, 4, 5	None
474	...	1-5,000+	8/30 to 9/20	Mixed strept.	3, 4, 5	50%
475	...	1-1,000+	9/ 6 to 9/20	Mixed strept.	3, 4, 5	None
476	10	1-10,000+	8/23 to 9/20	Mixed strept.	3, 4, 5, 6, 7	None
477	...	1-5,000±	8/23 to 9/13	Mixed strept.	3, 4, 5, 6	25%
478	...	1-500+	8/30 to 9/20	Mixed strept.	3, 4, 5, 6	50%
479	...	1-1,000+	9/ 4 to 9/20	Mixed strept.	3, 4, 5	None
480	186	1-10,000±	8/30 to 9/20	Mixed strept.	3, 4, 5, 6	Fair
481	102	1-5,000±	9/ 4 to 9/11	Mixed strept.	3, 4	50%
482	154	1-5,000+	9/ 4 to 9/11	Mixed strept.	3, 4	Fair

Since Patients 466, 469, 474, 475, 477, 478 and 479 had not been previously observed or treated by me, their cases will be considered together and not too much stress will be placed on the results. Patient 466 was 50 per cent. benefited and Patient 469 was not benefited by treatment with autogenous vaccines made from the nasal secretions. Patients 474 and 478 were 50 per cent, benefited, and Patient 477 was 25 per cent. benefited by the mixed streptococcus vaccine. Patients 475 and 479 were not benefited by the mixed streptococcus vaccine. The only conclusion to be drawn from these cases is that sometimes an autogenous nasal vaccine or a mixed streptococcus vaccine given during the hay-fever attack benefits somewhat an occasional patient but just as often this treatment fails.

12. Walker, I. C., and Adkinson, J.: Types of Streptococci Found in the Sputum of Bronchial Asthmatics, J. M. Research **40**:229, 1919.

The twelve following patients, however, since they were treated with ragweed pollen either during or preceeding the ragweed season in some year, give more defintie information. Patients 464 (184 and 439) and 472 (187) were relieved of symptoms while being treated with their autogenous nasal secretion vaccine, whereas both patients were only 50 per cent. benefited from preseasonal pollen treatment (Table 1, Patients 184 and 187) and one patient was not benefited at all by during-the-season pollen treatment (Table 10, Patient 439). In these two control cases it may be assumed that bacteria played some part, at least, in the cause of symptoms. Since Patients 468 (11), 471 (385), 473 (463) and 476 (10) were not benefited by vaccine treatment but all had been free from symptoms from ragweed pollen treatment, it is certain that bacteria played no part in the causation of their hay-fever symptoms. These four patients had been treated with ragweed pollen extract: Patients 468 (11) and 476 (10), preseasonal one year and were free from symptoms (Table 1, Nos. 10 and 11); Patients 471 (385), preseasonal three years in succession and was free from symptoms two years and practically free the third year (Table 6, No. 385); Patient 473 (463) treated during the season was free from symptoms (Table 10, No. 462). Patient 465 who was not benefited by either *Staphylococcus pyogenes albus* vaccine or by too little preseasonal treatment (Table 3, No. 264), and was only 50 per cent. benefited by considerable preseasonal treatment (Table 1, No. 181) gives no information with the exception that *Staphylococcus pyogenes albus* played no part in the causation of hay-fever symptoms in this case; this same organism was used in two cases already discussed, Patients 468 and 471, with no benefit. Patients 480 (186) and 482 (154) both became practically free from symptoms during mixed streptococcus vaccine treatment, whereas from preseasonal pollen treatment both were benefited only 75 per cent. (Table 1, Nos. 186 and 154); therefore, in these two cases streptococci probably played a considerable part in the causation of hay-fever symptoms. Patient 470 (185) was 75 per cent. benefited during treatment with *Staphylococcus pyogenes aureus* vaccine, whereas only a 50 per cent. benefit followed preseasonal pollen treatment (Table 1, No. 185), therefore *Staphylococcus pyogenes aureus* probably played some part in the causation of hay-fever symptoms in this case. Patient 481 (108) was 50 per cent. benefited during mixed streptococcus vaccine treatment, but was not improved by preseasonal pollen treatment (Table 1, No. 108); therefore, in this case it is quite evident that streptococci played a part in the causation of hay-fever symptoms.

The series of patients who were treated with bacterial vaccines is too small to justify sweeping conclusions, however, it does seem as though treatment with bacterial vaccines were beneficial for a few

hay-fever patients who are very sensitive to pollen. If a vaccine is to be used, the choice of bacteria would seem to be either an autogenous nasal or a mixed streptococcus vaccine. In the few cases in which considerable preseasonal pollen treatment is not very satisfactory, it is worth while to try during-the-season treatment with autogenous nasal secretion or a mixed streptococcus vaccine.

In Table 12 are presented eighteen patients who were treated with ragweed pollen both preceding and during the season. The first nine patients were given the usual preseasonal pollen treatment and then this treatment was discontinued. A little later, during the same season, these patients reported that they were having more or less hay-fever so that during-the-season treatment with pollens was then given as described in Table 10; in other words, the two methods of treatment were given to these patients. The other nine patients were treated with gradually increasing doses of the pollen extract, but the treatment

TABLE 12.—PRECEEDING AND DURING SEASON TREATMENT WITH RAGWEED POLLEN

Patient	Previous No.	Tests Before Treatment	Dates of Treatment	Treatment in Cubic Centimeters With Dilution of Ragweed Pollen	Result of Treatment
483	14	1-1,000±	8/21 to 9/10	1-5,000 = 0.15, 0.3, 0.45, 0.55	50%
484	308	1-1,000±	8/23 to 9/10	1-5,000 = 0.15, 0.3, 0.45	Same
485	18	1-5,000±	8/22 to 9/ 3	1-5,000 = 0.1, 0.2, 0.3	Same
486	314	1-5,000±	8/21 to 9/10	1-10,000 = 0.15, 0.25; 1-5,000 = 0.15, 0.25	None
487	309	1-10,000±	8/26 to 9/10	1-10,000 = 0.15; 1-5,000 = 0.1, 0.2	Worse
488	317	1-1,000±	8/20 to 9/ 3	1-1,000 = 0.15; 1-500 = 0.15, 0.15	Same
489	33	1-5,000+	8/22 to 9/18	1-10,000 = 0.15, 0.25, 0.35; 1-5,000 = 0.2, 0.2	50%
490	320	1-5,000±	8/28 to 9/10	1-10,000 = 0.15, 0.25, 0.35	None
491	35	1-5,000±	8/21 to 9/10	1-5,000 = 0.15, 0.25, 0.35	Same
492	...	1-5,000±	7/18 to 9/10	Usual treatment including 1-500 = 0.55	None
493	...	1-10,000±	7/ 7 to 9/20	Usual treatment including 1-500 = 0.55	50%
494	...	1-20,000±	6/30 to 9/13	Usual treatment including 1-500 = 0.65	75%
495	...	1-10,000±	6/14 to 9/ 4	Usual treatment including 1-500 = 0.25	75%
496	...	1-5,000±	7/ 3 to 9/13	Usual treatment including 1-500 = 0.25	75%
497	469	1-5,000+	7/10 to 9/20	Usual treatment including 1-500 = 0.25	50%
498	...	1-10,000±	7/ 3 to 9/ 4	Usual treatment including 1-500 = 0.45	Fair
499	...	1-5,000±	7/ 3 to 9/ 4	Usual treatment including 1-500 = 0.3	50%
500	...	1-10,000±	7/10 to 9/20	Usual treatment including 1-500 = 0.25	50%

was begun so late preseasonally that not enough treatment would have been given had treatment been discontinued at the onset of pollination; therefore, the usual preseasonal treatment, using gradually increasing doses, was continued on through the season of pollination. For example, Patient 492 was treated with gradually increasing amounts of ragweed pollen extract from July 18 to September 10 inclusive; the usual preseasonal treatment was begun preseasonally and continued into or through the season of pollination.

Patients 483 and 489 were not benefited by preseasonal treatment (Table 1, Nos. 14 and 33); they were then given during-the-season treatment, as indicated in Table 12, with the result that they were 50 per cent. benefited. Patients 485 and 491 were benefited 75 and 50 per cent., respectively, following preseasonal treatment (Table 1,

Nos. 18 and 35); they were then given during-the-season treatment, as indicated in Table 12, with no apparent change in their symptoms. Patients 484, 486, 488 and 490 were all unimproved by during-the-season treatment following the preseasonal treatment (as indicated in Table 4, Nos. 308, 314, 317 and 320) which in two cases failed to benefit and in the two others there was a 50 per cent. benefit. The remaining patient (487 was not as much benefited while being treated during the season as he had been by preseasonal treatment (Table 6, No. 399). Therefore, in only two of these nine cases did during-the-season treatment improve the results already obtained from preseasonal treatment, but since these two patients were not benefited by preseasonal treatment (Table 1, Nos. 14 and 33) and became 50 per cent. benefited by during-the-season treatment, the latter treatment was worth trying after the former had failed; in other words, two failures were changed to 50 per cent. benefit.

The remaining nine patients were treated according to the preseasonal schedule, but treatment was begun very late (in July) and continued into the hay-fever season. Although this is the first time this method of pollen treatment has been mentioned in this paper, it has been used extensively in the past by many investigators. The results from this method of treatment, as indicated in Table 12, show that no patients were entirely free from symptoms; one patient, or 11 per cent., was practically free; one third of the patients were 75 per cent. benefited; 44 per cent. were 50 per cent. benefited, and one patient, or 11 per cent., was not benefited. Of course, this series of cases is much too small to warrant conclusions, yet it would seem fair to say that this method of treatment is preferable to during-the-season treatment alone but not as desirable as the regular preseasonal treatment which is begun early enough to permit of its discontinuance just prior to the season of pollination.

Hay-Fever Caused By the Pollen of Trees.—So far in this paper we have been concerned with the two pollen seasons, namely, August and September (ragweed) and May to August (the grasses). There is a third and earlier pollen season which begins in March and continues into June during which time various trees pollinate. Silver maple often pollinates in February; the other maples, birches, willows and hazel nut pollinate in late March or early April; the poplars, Juniper, cottonwood and elm pollinate during April; the oaks, ash, bayberry and hickory pollinate during May; the pines pollinate in late May and early June, and the fruit trees pollinate in May. I have observed twelve patients who were sensitive to and had hay-fever from the pollen of trees. One patient had hay-fever caused by the pollen of apple blossoms, and he was free from symptoms following preseasonal treatment with its pollen extract. One patient, who was

sensitive to the pollen of the oak and maple, and another, who was sensitive to the pollen of the willow, were both free from symptoms following preseasonal treatment with these pollen extracts. Patients not treated were those sensitive to the following tree pollens: one patient, to poplar tree pollen; one, to pine tree pollen; two, to ash; one, to willow; two, to both willow and poplar, and one to willow, poplar and ash. Since the season of pollination of the individual trees continues only from a few days to two weeks at the most, it does not seem essential that treatment be given.

Other Pollens that May Cause Hay-Fever.—It has been shown in this paper that the chief causes of hay-fever occurring in the New England States were the pollens of ragweed, timothy and June grass; that an occasional cause is the pollen of the rose and redtop grass and of various trees. There is, however, almost an unlimited list of pollens that may at any time, but probably rarely, cause hay-fever. Therefore, for those who treat a large number of hay-fever patients and for those who fail to obtain satisfactory results from treatment with the common pollens mentioned, it is advisable to have a very extensive assortment of pollens. As a rule, however, it would seem to be sufficient to warn the ragweed patients that they should not smell of golden rod, golden glow, sunflower, poppy, aster, chrysanthemum and the like that pollinate during the ragweed season. The grass cases may be warned to avoid close contact with clover, lilies, daisy, dandelion, rose, lawn grass, orchard grass, corn and the like that pollinate during the grass season. In certain localities in this country it may be necessary to treat with the pollen extracts of the various grains, with sunflower or what not but this necessity is not universal and is limited to the various localities where exposure to these particular pollens is unavoidable.

Other Parts of Plants that May Cause Hay-Fever.—The leaves of certain plants and trees may cause hay-fever. The under surface of some leaves has a fine hairy growth, and these fine hairs may cause hay-fever. I have observed one patient who had hay-fever from and was sensitive to the hairs of the willow tree leaf; treatment with an extract of these leaves prevented hay-fever. Another patient was sensitized to and had hay-fever from the plantain leaf. It is quite probable that the plane tree, the common shade tree in London, may cause hay-fever. Such instances, however, are extremely rare and need not be considered, as a rule.

Foods May Cause Seasonal Hay-Fever.—Seasonal hay-fever, due primarily to foods, has not come to my notice. However, during their season many hay-fever patients find that certain foods aggravate their symptoms, whereas these same foods may be eaten without symptoms at a time when they are not accustomed to have hay-fever,

and they can eat the foods during their hay-fever season, provided they have had sufficient pollen treatment to protect them against the particular pollen that primarily causes their hay-fever. These foods are usually the fruits, and they have no apparent relationship to the causative pollen. Among the usual fruits should be mentioned peach, melon and apple. Green corn and the use of beer and wine often aggravate ragweed hay-fever, but they do not aggravate grass pollen hay-fever as one would expect to be the case; celery sometimes acts similarly. With the peach it is often the skin that causes trouble, whereas the pulp usually does not. The cooking of the fruits often renders them inert.

Animal Emanations May Cause Seasonal Hay-Fever.—The patient who is sensitive to animal emanations usually has symptoms on exposure to the animal at any and all times of the year; occasionally, however, such a patient has symptoms only from exposure to the animal during the spring and summer, when the animal is shedding, moulting or perspiring profusely.

Bacteria May Cause Seasonal Hay-Fever.—The possibility of bacterial infection as a complication of or secondary to pollen sensitization has already been discussed, and the possibility of bacterial infection as a primary cause of hay-fever in patients who are not sensitive to pollens must be considered. Each year I examine three or four patients who have seasonal hay-fever, but who are not sensitive to any of the pollens; therefore, these patients are treated with their autogenous nasal secretion vaccine.

REPORT OF CASES

Case 1.—L. W., a woman, aged 35, has had hay-fever from August first to the end of October for three years. Her symptoms are sneezing, running of the nose and some wheezing.

Not only were the skin tests with pollens negative, but she also failed to give an ophthalmic test, and snuffing the whole pollen of ragweed and dropping a concentrated solution of ragweed pollen extract into her nose failed to provoke symptoms.

The patient was treated with an autogenous vaccine, made from her nasal secretion, in gradually increasing amounts, beginning with 300 million streptococci, from June 25 to Oct. 11, 1919. At the end of the season, she reported that in previous summers she had always lost three weeks of sleep, whereas during the past summer she had lost only one week of sleep, and that her days had been quite free from symptoms.

In June, 1920, she reported that her hay-fever had begun about three weeks previously. She was again treated as previously, from June 7 to July 12, when she discontinued treatment because she had been entirely free from symptoms for the past three weeks and she continued to be free during the summer.

Case 2.—H. S. M., a woman, aged 29, has had hay-fever for five years, from August 15 to the first frost. The symptoms are sneezing, tickling in the throat and running of the nose, alternating with stuffing up of the nose. She was first seen in June, 1918, and her symptoms had already begun this year, much earlier than usual.

She was treated with gradually increasing amounts of an autogenous vaccine made from her nasal secretion, from June 21 to August 14; the first treatment was 300 million streptococci. In the winter following this treatment, she reported that she had had only six bad days of hay-fever during the whole summer; she claimed that she had been markedly free from hay-fever.

The patient returned the following year, in May, 1919, and reported that her sneezing and running of the nose had just begun again. She was treated again with a new autogenous vaccine in a similar manner as was done the preceding year. During the first six weeks of treatment, she had occasional attacks of hay-fever, but not as bad as usual, during the remainder of the summer she was practically free from hay-fever.

Case 3.—E. L. T., a woman, aged 30, has had hay-fever for four years, from August to the first frost. Her hay-fever is worse at night and prevents sleep. Her present attack began August 26. She was not sensitive to pollens.

She was treated from September 1 to October 6, inclusive, with an autogenous nasal secretion vaccine consisting of *Staphylococcus pyogenes aureus* in gradually increasing amounts, beginning with 300 million bacteria; during the season, she was given treatment with vaccines. Following the first treatment, she was a little better, and following each succeeding treatment she was free from symptoms for four days but had considerable hay-fever the two days preceding each treatment.

These three patients would seem to prove that there are cases of seasonal hay-fever not caused by pollens but caused by bacteria and that treatment with autogenous vaccines made from their nasal secretions is often very effective. It is noted that in these nonsensitive pollen cases of hay-fever there was an absence of eye symptoms, as noted in a previous paper.[13]

Hay-Fever Caused By Olfactory Irritants or Pseudo-Hay-Fever.—Goodale [14] called attention to the fact that during pollen seasons certain individuals who are sensitive to and have hay-fever from pollens also have vaso-motor symptoms ranging from sneezing to asthmatic attacks due to the fragrance of certain heavily scented flowers that have no pollen or to which pollen the individual is not sensitive. He considers that the symptoms are reflex and that the path of transmission is along the olfactory nerve. The flowers most commonly responsible are lilies, hyacinths, sweet peas, lilacs, honey suckle and peonies.

I classify the causes of symptoms as mechanical, chemical, odorific and thermal. Among the mechanical causes any kind of dust is the most frequent cause, more especially sweeping dust and hay dust; fine powder, such as talcum and the like, is also a frequent cause. Among the chemical irritants, soap powder, lye and ammoniacal fumes are very frequent causes. Among the odorific irritants, heavily scented perfumes, face powders, musty air and stable odors are frequent causes. Thermal irritants concern sudden changes of temperature,

13. Walker, I. C.: Frequent Causes and the Treatment of Perennial Hay-Fever, J. A. M. A. **75**:782 (Sept. 18) 1920.

14. Goodale, J. L.: The Present Status of Immunization in Hay-Fever, Boston M. & S. J. **179**:293, 1918.

as in going from warm air to extreme cold, from moist air to very dry air, and exposure to drafts; a very frequent history is that of a paroxysm of sneezing with or without running of the nose on retiring and arising. The mechanism seems to be a reflex due to the sudden exposure of the warm and protected skin of the body to cold air, as in getting out of bed and in undressing, during which acts the warm body surface is suddenly and momentarily exposed to cool air; in other words, there is a mild chilling of the body surface.[15] The same mechanism holds for many who take cold easily. Appropriate pollen treatment for those who are sensitive usually relieves these symptoms.

TABLE 13.—Preseasonal Treatment with Ragweed Pollen Extract

Results	1917		1918		1919		1920		Total	
	No. of Patients	Percentage of Total Patients	No. of Patients	Percentage of Total Patients	No. of Patients	Percentage of Total Patients	No. of Patients	Percentage of Total Pa. tients	No. of Patients	Percentage of Total Patients
Good	19	70	26	32	52	37	13	7	110	25
Fair	1	4	9	11	32	23	48	25	90	20
75%	4	15	23	28	31	22	82	43	140	32
50%	3	11	16	20	15	10	45	23	79	18
None	0	0	7	8½	10	7	3	1½	20	4½
Total	27	..	81	..	140	..	191	..	439	
B. Preseasonal Treatment with Grass Pollens										
Good	8	80	10	66	13	72	5	14	36	46
Fair	0	0	3	20	1	5	7	20	11	14
75%	1	10	2	13	2	11	12	33	17	21.8
50%	1	10	0	0	2	11	8	23	11	14
None	0	0	0	0	0	0	3	8½	3	4
Total	10	..	15	..	18	..	35	..	78	

SUMMARY

The methods used by me in testing and treating seasonal hay-fever and the seasons of pollination of the causative pollens are described in detail. Eight tables are then presented to illustrate the benefits obtained by preseasonal pollen treatment. Table 3 shows the unsatisfactory results obtained by giving less than three doses of the 1:500 dilution of the pollen extract, and the other seven tables show the good results obtained when more than three doses of the 1:500 dilution, or preferably one or more treatments with the 1:100 dilution of the pollen extract are given. Tables 1 and 2 deal with a single season's treatment, and Tables 4 to 8 inclusive, deal with two or more successive seasons' treatment. In general, the greater the amount of treatment given, the better the symptomatic results and the greater is the reduction

15. Mudd, S., and Grant, S. B.: Reactions to Chilling of the Body Surface. J. M. Research **40**:53, 1919.

in the positiveness of the skin test. Table 13 is a composite of Table 1 to 8 inclusive, with the exception of Table 3 which concerns insufficient treatment. It shows the results obtained from preseasonal treatment with ragweed pollen and with the grass pollens for each year and the results for all four years.

The percentage of results varies somewhat for different years; this is due, in great part, to variation in treatment. The average results for all four years following preseasonal ragweed treatment show that nearly 50 per cent. of the patients had little or no symptoms, and a third of the others were 75 per cent. benefited; whereas in only 4.5 per cent. of all of the cases was there failure from treatment. In some of the individual years, treatment showed much better results than this. The average results of treatment with the grass pollen group of cases shows that 60 per cent. of the patients had little or no symptoms, and 21.8 per cent. were 75 per cent. benefited, whereas 4 per cent. were not benefited. In some of the individual years, treatment gave much better results than in other years, and this variation was due to varying treatment. Unless patients return for future treatment, it is very difficult to get in touch with them in order to find out the permanency of relief from treatment. In four cases, however, it has been possible to learn that more or less permanency of benefit follows sufficient preseasonal treatment. Case 11, treated in 1917, was also free from symptoms in 1918 and 1919 without any treatment, but in 1920 this patient had severe symptoms. Case 1 was free from symptoms following treatment but has not been heard from since. Case 70 was free from symptoms following treatment in 1919, and was also free from symptoms in 1920, without treatment. Case 312, free from symptoms in 1918 and 1919 following treatment both years, had no symptoms in 1920 without treatment.

Tables 9 and 10 deal with during-the-season pollen treatment, and the general conclusion is that during-the-season pollen treatment with the grasses is worth doing but is not as satisfactory as the preseasonal treatment, and that during-the-season treatment with ragweed pollen is very unsatisfactory. Treatment for the early type of hay-fever seems to yield better results than treatment for the late type. This is probably due to the fact that there are several causes for the early type of hay-fever such as June grass, rose and timothy pollen all of which pollinate at different times and each over a short interval and it is usually only one of these pollens that cause symptoms. Therefore, the actual cause of early hay-fever is present a short time, whereas ragweed which is practically always the only cause of late hay-fever pollinates as long a time as all of the early pollens together, and a much longer time than any one of the early pollens.

Table 11 presents pollen sensitive patients who were treated with bacterial vaccines, and there is evidence that bacteria may, in some pollen sensitive cases, play a part in the cause of hay-fever symptoms. With those patients who are not sufficiently benefited by supposedly satisfactory preseasonal pollen treatment, treatment with autogenous nasal vaccines is indicated during the pollen season.

Table 12 presents cases treated with ragweed pollen preceding and during the season. In the case of patients not much benefited by satisfactory preseasonal pollen treatment, small doses of the pollen protein given during the season may produce benefit. In the case of those patients who present themselves too late for sufficient preseasonal treatment, gradually increasing amounts of the pollen protein may be given throughout the hay-fever season. The results from this kind of treatment seem to be better than those from during-the-season treatment alone with either pollens or bacteria but not nearly as satisfactory as the results obtained from preseasonal pollen treatment that is begun early enough to permit of its discontinuance before the season of pollination.

Since close contact with pollens that are closely related to the causative pollen, the eating of fruits, and certain olfactory irritants may all complicate the cause and the treatment of hay-fever, it is not remarkable that hay-fever treatment does not always afford entire protection.

Other causes of seasonal hay-fever that must be considered are tree pollens, animal emanation and bacteria.

CONCLUSIONS

Satisfactory preseasonal pollen treatment yields excellent results in seasonal hay-fever. By satisfactory treatment is meant five or six treatments with a 1 : 500 dilution of the pollen extract, or, better still, two or three treatments with a 1 : 100 dilution of the pollen extract.

When preseasonal pollen treatment fails, sometimes benefit results from during-the-season treatment with pollens and sometimes from during-the-season treatment with an autogenous nasal secretion vaccine. During the season treatment with pollens without preseasonal treatment is not very satisfactory although such treatment for the early type of hay-fever is worth doing provided for some reason or other it is not possible to give preseasonal treatment.

Treatment that of necessity must begin late preseasonally may be continued on through the pollen season with better results than those obtained by during-the-season treatment alone, but with much less

beneficial results than those obtained by begining preseasonal treatment early enough to permit of its discontinuance before the season of pollination begins.

Although in the New England States the pollen of ragweed (dwarf variety) is practically always the cause of late hay-fever (August and September), and the pollen of timothy grass is the cause of probably 90 per cent. of the early hay-fever (June and July), in other localities other pollens may play a great part in the cause of either type of hay-fever. For this reason it is essential that other observers publish their tests, results and treatment in detail in order to learn the causative pollens and proper treatment in various localities.

In the New England States the pollen of rose and redtop grass occasionally cause early hay-fever, and treatment occasionally has to be given with these. The pollen of June grass is a more or less common cause of early hay-fever but when the season of its pollination is very early, unless the treatment is begun very early, too little treatment can be given with it to be of benefit, and when its pollination is very late sufficient treatment with timothy pollen has been given to protect against June grass pollen exposure.

Treatment with a combination of timothy and June grass pollens was not successful in my hands because of insufficient treatment with both pollens; the addition of June grass pollen retarded the amount of treatment that otherwise would have been given with timothy alone. Another illustration of the undesirability of mixed pollen treatment is noted with those patients who have both the early and the late types of hay-fever. In these cases, during the month of May and part of June, large amounts of timothy pollen extract should be given together with small amounts of ragweed pollen extract, and the result in these cases is rather poor because there is a tendency to restrict the timothy treatment for fear of producing anaphylaxis from the combination of two pollens to which the patient is sensitive. In other words, treatment with a combination of pollens either diminishes the amount of treatment that is required with one or all of them or pushing the treatment with the combination leads to the danger of anaphylaxis. For either or both of these reasons, I see no benefit to be derived from mixed pollen therapy. As regards the early type of hay-fever, I consider it best to treat preseasonally with timothy or the chief causative pollen and, if necessary to treat during the season with June grass pollen.

Since intimate exposure to other pollens which may be attributing causes of hay-fever, the eating of fruits during the hay-fever season, the possibility that bacteria play a part in the cause of hay-fever and

the exposure to olfactory irritants may all aggravate the symptoms of hay-fever, it is not remarkable that hay-fever treatment is not perfect.[16]

16. Selfridge,[17] Koessler[18] and Scheppegrell[19] have published the prevailing pollens in their respective localities, namely, California, Illinois and the Southern States and they have designated those pollens that seem to be the chief causes of hay-fever in these localities. It is desirable that others in various localities do likewise.

17. Selfridge, G.: Spasmodic Vasomotor Disturbances of the Respiratory Tract, with Special Reference to Hay-Fever, California State J. M. **16**:164, 1918.

18. Koessler, K. K.: The Specific Treatment of Hay-Fever (Pollen Disease), Billings-Forchheimer Therapeusis of Internal Diseases, **5**: New York, D. Appleton & Co.

19. Scheppegrell, W.: Hay-Fever in the Southern States, Southern M. J. **9**:614, 1916.

SOME URINARY CHANGES IN NORMAL INDIVIDUALS ON THE PELLAGRA PRODUCING EXPERIMENTAL DIET *

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Many of the pellagra patients admitted to the Pellagra Hospital in 1917 gave a history of using diets which consisted mainly of cereals, fat pork, molasses and greens, with little, if any, animal protein. On such a type of diet, Goldberger and Wheeler [1] experimentally produced pellagra in the human subject at the Rankin Farm, Mississippi State Penitentiary. To test the pellagra producing diet as regards its effect on the main urinary constituents, six normal people were placed on this Rankin Farm experimental diet as given for the week ending Aug. 8, 1915. It was intended to run the experiment for at least several weeks. Unfortunately, on the fifth day of the period of the experimental diet, the water supply of the laboratory froze and the experiment was brought to an end. Accordingly, only the data for four or five days, on the diet mentioned, are available, but these data are of some interest. The diet used was as follows:

BILL OF FARE, WEEK ENDING AUG. 9, 1915

August 2

Breakfast: Biscuits, fried mush, grits and brown gravy, sirup, coffee with sugar.
Dinner: Corn bread, cabbage, sweet potatoes, grits, sirup.
Supper: Fried mush, biscuits, rice, gravy, cane sirup, coffee, sugar.

August 3

Breakfast: Biscuits, mush, rice, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

August 4

Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, rice, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee and sugar.

August 5

Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, rice, gravy, sirup, coffee, sugar.

August 6

Breakfast: Biscuits, mush, rice, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

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* From the Pellagra Hospital, U. S. Public Health Service.

1. Public Health Rep. **30**: No. 46, Nov. 13, 1915; Bull. 120, Hyg. Lab., Washington, D. C.

TABLE 1.—URINARY DATA OF NORMAL PEOPLE ON THE PELLAGRA PRODUCING EXPERIMENTAL DIET

Subject	Weight, Kg.	Date	Diet	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Urea, Gm.	Urea Nitrogen, Gm.	Creatinin, Gm.	Creatinin Nitrogen Gm.	Urea N per Cent. of Total Nitrogen	NH3N per Cent. of Total Nitrogen
1	...	Dec. 2-3	Normal										
		Dec. 3-4	Mixed	770	1.025	8.410	0.316	13.749	6.416	1.247	0.464	76.29	3.76
		Dec. 4-5	Diet	1 410	1.019	11.822	0.436	21.429	10.000	1.503	0.559	84.59	3.69
	76 2	Dec. 5-6	Diet	1,000	1.016	9.973	0.432	18.433	8.602	1.379	0.513	86.25	4.33
1	...	Dec. 6-7	Rankin farm pellagra producing diet	690	1.031	7.403	0.352	11.902	5.414	1.118	0.416	73.13	4.75
		Dec. 7-8	Rankin farm pellagra producing diet	540	1.033	5.972	0.462	8.872	4.140	1.007	0.397	69.32	7.74
		Dec. 8-9	Rankin farm pellagra producing diet	600	1.031	6.196	0.437	9.266	4.324	1.034	0.384	69.78	7.05
	75.0	Dec. 9-10	Rankin farm pellagra producing diet	600	1.032	6.248	0.419	8.057	3.760	.....	.....	60.18	6.71
		Dec. 10-11	Rankin farm pellagra producing diet	5.0	1.074	5.622	0.502	6.585	3.073	.....	.....	54.66	8.93
2	52.6	Dec. 2-3	Normal	1,650	1.018	10.831	0.346	20.148	9.402	1.285	0.478	86.81	3.19
	52.6	Dec. 3-4	Normal	1,400	1.018	12.433	0.459	20.109	9.426	1.418	0.527	75.81	3.69
	52.6	Dec. 4-5	Normal	930	1.025	11.414	0.513	20.503	9.610	1.256	0.467	84.19	4.49
	52 7	Dec. 5-6	Normal	1,440	1.022	12.590	0.512	23.510	10.971	1.341	0.498	87.14	4.07
2	....	Dec. 6-7	Pellagra producing diet	1,190	1 020	8 304	0.391	14.497	6.765	1.252	0.465	81.47	4.71
		Dec. 7-8	Pellagra producing diet	1,160	1.0 0	5.759	0.347	9.056	4.226	1.342	0.499	73.38	6.02
		Dec. 8-9	Pellagra producing diet	1,125	1.013	5.447	0.339	8.734	4.076	1.125	0.418	74.83	6.22
	51.4	Dec. 9-10	Pellagra producing diet	700	1.026	5.984	0.356	9.281	4.331	.....	.....	72.38	5.95
		Dec. 10-11	Pellagra producing diet	750	1.0 3	6.319	0.357	.....	.....	.....	.....	.....	5.65
3	....	Dec. 2-3	Normal	1.080	1.029	11.408	0.521	19.046	8.888	1.286	0.478	77.91	4.57
		Dec. 3-4	Normal	1,160	1.028	11.421	0.499	19.494	9.097	1.305	0.485	79.65	4.37
		Dec. 4-5	Normal	1,670	1.020	12.300	0.599	21.607	10.083	1.470	0.546	81.98	4.87
	63.7	Dec. 5-6	Normal	1,560	1.021	12.585	0.581	24.225	11.305	1.487	0.553	89.83	4.62
3	...	Dec. 6-7	Pellagra producing diet	920	1.032	8.805	0.472	15.547	7.255	1.096	0.407	82.40	5 36
		Dec. 7-8	Pellagra producing diet	950	1.028	6.917	0.448	12.337	5.757	1.304	0.485	83.23	6.48
		Dec. 8-9	Pellagra producing diet	1,275	1.017	6.313	0.460	9.587	4.474	.....	.....	70.87	7.29
	65.3	Dec. 9-10	Pellagra producing diet	800	1.029	6.302	0.530	8.276	3.862	.....	.....	61.28	8.41
		Dec. 10-11	Pellagra producing diet	875	1.023	7.755	0.436	8.488	3.961	.....	.....	51.08	5.62

4	....	Dec. 3-4	Normal.....	940	1.025	10.292	0.340	16.479	7.690	1.384	0.514	74.71	3.30
	55.9	Dec. 5-6	Normal.....	1,560	1.014	7.277	0.225	13.406	6.256	0.918	0.341	85.97	3.09
4	. . .	Dec. 6-7	Pellagra producing diet..	1,470	1.020	6.548	0.284	11.413	5.326	1.417	0.527	81.34	4.34
		Dec. 7-8	Pellagra producing diet..	900	1.023	6.280	0.302	11.379	5.310	1.278	0.475	84.55	5.76
		Dec. 8-9	Pellagra producing diet..	1,485	1.016	6.704	0.317	11.465	5.350	1.002	0.372	79.10	4.54
	54 4	Dec. 9-10	Pellagra producing diet..	1,040	1 012	5.007	0.302	7.710	3.568	.....	.....	71.86	6.03
		Dec. 10-11	Pellagra producing diet..	600	1.027	5.433	0.318	6.879	3.210	.....	.....	59.09	5.85
5	....	Dec. 3-4	Normal.....	885	1.023	9.959	0.464	16.209	7.564	0.885	0.329	75.95	4.66
		Dec. 4-5	Normal.....	1,210	1.021	14.383	0.581	26.392	12.316	1.167	0.434	85.63	4.04
	49.3	Dec. 5-6	Normal.....	815	1.031	13.511	0.566	20.705	9.662	1.031	0.383	71.51	4.19
		Dec. 6-7	Pellagra producing diet..	1,270	1.022	9.355	0.389	17.199	8.026	0.989	0.368	85.79	4.16
		Dec. 7-8	Pellagra producing diet..	1,125	1.024	5.647	0.369	8.839	4.125	0.930	0.346	73.05	6.53
		Dec. 8-9	Pellagra producing diet..	1,675	1.010	4.720	0.348	8.250	3.850	0.909	0.360	81.57	7.37
	48.5	Dec. 9-10	Pellagra producing diet..	1,010	1 023	5.037	0.276	7.423	3.464	.....	.....	68.77	5.48
6	....	Dec. 2-3	Normal.....	900	1.028	9.434	0.448	15.628	7.296	1.572	0.584	77.31	4.75
		Dec. 3-4	Normal.....	700	1.034	7.529	0.365	11.490	5.362	1.232	0.458	71.22	4.85
		Dec. 4-5	Normal.....	575	1.033	8.127	0.394	13.018	6.075	1.109	0.412	74.75	4.85
	56.9	Dec. 5-6	Normal.....	500	1.035	7.908	0.443	13.485	6.293	1.080	0.404	79.58	5.60
6	....	Dec. 6-7	Pellagra producing diet..	600	1.034	7.412	0.457	12.885	6.013	1.118	0.416	81.13	6.17
		Dec. 7-8	Pellagra producing diet..	1,190	1.021	6.761	0.532	12.780	5.964	1.220	0.453	88.21	7.87
		Dec. 8-9	Pellagra producing diet..	1,415	1.014	6.039	0.457	7.929	3.700	0.980	0.364	61.27	7.57
	57.0	Dec. 9-10	Pellagra producing diet..	1,200	1.016	5.679	0.381	8.237	3.844	.....	.....	67.69	6.71
		Dec. 10-11	Pellagra producing diet..	560	1.028	4.565	0.285	5.803	2.708	.....	.....	59.32	6.24

TABLE 2.—URINE DATA OF NORMAL PEOPLE ON THE RANKIN FARM PELLAGRA PRODUCING EXPERIMENTAL DIET

	Volume, C.c.	Specific Gravity	Total Nitrogen, Gm.	Ammonia Nitrogen, Gm.	Urea Nitrogen, Gm.	Creatinin, Gm.	Creatinin Nitrogen, Gm.	Urea N per Cent. of Total Nitrogen	NH_3N per Cent. of Total Nitrogen	Average Weight, Kg.	Creatinin Coefficient
Diet Dec. 2-6											
Normal mixed diet, average of 20 tests	1,137	1.024	10.680	0.452	8.616	1.208	0.471	80.35	4.25	59.1	7.88
Pellagra diet, average 24 tests, Dec. 6-10	1,042	1.023	6.454	0.395	4.873	1.132	0.421	74.86	6.22		
Pellagra diet, average of last test after 4 days on the diet	907	1.023	5.710	0.377	3.810	1.069 (3d day)	0.397 (3d day)	67.03	6.55	58.3	7.05
Average for 26 pellagra patients in active pellagra; severe, moderate, mild cases	1,158	1.020	6.214	0.519	4.457	0.751	0.279	71.81	8.453	47.46	5.82
Average of same 26 patients; cured	1,420	1.020	10.588	0.605	8.665	0.856	0.318	81.64	5.79	49.397	6.34

August 7

Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, rice, sirup.
Supper: Biscuits, mush, grits, gravy, sirup, coffee, sugar.

August 8

Breakfast: Biscuits, mush, grits, gravy, sirup, coffee, sugar.
Dinner: Corn bread, collards, sweet potatoes, grits, sirup.
Supper: Biscuits, mush, rice, gravy, sirup, coffee, sugar.

Each person was allowed to eat as much of the diet as he or she pleased. With one exception, Subject 1, all the volunteers were males.

The methods of analysis employed were: for total nitrogen, Kjeldahl; for ammonia, Folin's [2] method as modified by Steel [3]; creatinin by Folin's method [4]; urea by Folin and Denis' method,[5] using Jack bean as a source of urease and a reaction temperature of from 50 to 55 C.

The individual records for volume, specific gravity, total nitrogen, ammonia nitrogen, urea and urea nitrogen, creatinin and creatinin nitrogen, the ratio of urea nitrogen and ammonia nitrogen to total nitrogen are given in Table 1, and the average for the fourth day on the pellagra producing experimental diet are given in Table 2. By reference to these tables, it will be noted that on changing from the ordinary mixed diet to the Rankin Farm pellagra producing diet there was a marked change in the urine. The average volume decreased; the total nitrogen and urea nitrogen decreased markedly, the urea nitrogen especially; the ammonia decreased slightly. The ratio of urea nitrogen to total nitrogen was markedly lowered, the ammonia ratio increased.

The findings recorded for the fourth day on the diet are comparable to those which obtain in the urine of pellagra patients in the active stage of the disease,[6] especially for total nitrogen, urea, and, to a degree, for ammonia and are such as would obtain on a low protein diet as found by Folin.[7]

Many thanks are due the volunteers on this diet and especially to Mr. R. E. Stanton for his assistance.

2. Am. J. Physiol. **13**:45, 1905.
3. J. Biol. Chem. **8**:365, 1910.
4. Ztschr. f. Physiol. Chem. **41**:223, 1904.
5. J. Biol. Chem. **26**:501, 1916.
6. Sullivan, Stanton, and Dawson: Metabolism in Pellagra: A Study of the Urine. Archives Intern. Med. **27**:387, 1921.
7. Laws Governing the Chemical Composition of Urine. Am. J. Physiol. **13**:67, 1905.

Book Reviews

TUBERCULOSIS OF CHILDREN, ITS DIAGNOSIS AND TREATMENT. By HANS MUCH, M.D., translated from the German by MAX ROTHSCHILD, M.D. Ed. 1. Pp. 156. New York: The Macmillan Company, 1921.

This volume contains very little as to the diagnosis of tuberculosis, but emphasizes particularly the types of immunity and immunologic reactions in tuberculosis and gives a new method of treatment, based largely on the use of "partial antigens." Many new ideas are advanced, which make the book most interesting. The author adheres to the old idea that erythema nodosum is a tuberculid, to which the reviewer takes exception. The translator, at least, makes the common mistake of using the words "tubercular" and "tuberculous" synonymously. The book should be read by all students of immunology and by those particularly interested in the treatment of tuberculosis.

Fifty cents each will be paid for the following issues of the Archives of Internal Medicine: January, March, June, August, 1918. January and July, 1916; November, 1915; January, 1911; July, 1909. AMERICAN MEDICAL ASSOCIATION, 535 North Dearborn Street, Chicago, Ill.